OPEN

Driving Performance Under Alcohol in Simulated Representative Driving Tasks

An Alcohol Calibration Study for Impairments Related to Medicinal Drugs

Ramona Kenntner-Mabiala, PhD, Yvonne Kaussner, PhD,* Monika Jagiellowicz-Kaufmann, MSc,* Sonja Hoffmann, MSc,* and Hans-Peter Krüger, PhD*†‡*

Abstract: Comparing drug-induced driving impairments with the effects of benchmark blood alcohol concentrations (BACs) is an approved approach to determine the clinical relevance of findings for traffic safety. The present study aimed to collect alcohol calibration data to validate findings of clinical trials that were derived from a representative test course in a dynamic driving simulator. The driving performance of 24 healthy volunteers under placebo and with 0.05% and 0.08% BACs was measured in a double-blind, randomized, crossover design. Trained investigators assessed the subjects' driving performance and registered their driving errors. Various driving parameters that were recorded during the simulation were also analyzed. Generally, the participants performed worse on the test course ($P < 0.05$ for the investigators' assessment) under the influence of alcohol. Consistent with the relevant literature, lane-keeping performance parameters were sensitive to the investigated BACs. There were significant differences between the alcohol and placebo conditions in most of the parameters analyzed. However, the total number of errors was the only parameter discriminating significantly between all three BAC conditions. In conclusion, data show that the present experimental setup is suitable for future psychopharmacological research. Thereby, for each drug to be investigated, we recommend to assess a profile of various parameters that address different levels of driving. On the basis of this performance profile, the total number of driving errors is recommended as the primary endpoint. However, this overall endpoint should be completed by a specifically sensitive parameter that is chosen depending on the effect known to be induced by the tested drug.

Key Words: traffic safety, driving ability, driving fitness, psychomotor performance, side effect

(*J Clin Psychopharmacol* 2015;35: 134–142)

Modern driving simulation provides an experimental setting that allows for a safe and relatively realistic investigation of drug-related deficits on driving behavior. Major advantages of driving simulation are that dangerous situations can be systematically designed, presented, and reproduced.[1] Furthermore, compensatory behavior can be practiced as if participants were in real traffic.[2] One disadvantage of driving simulators is, however, that drivers may experience simulator sickness. Roughly 40% to 50% of test drivers who are not familiar with simulator driving report symptoms of simulator sickness. This disadvantage is easily remedied, however, if drivers complete familiarization sessions in the simulator; 90% of all test drivers who completed such sessions do not experience any symptoms of simulator sickness.[3]

To validate and determine the clinical relevance of drug-induced effects on driving performance, the comparison of those effects with effects of benchmark blood alcohol concentrations (BACs) is an approved and face-valid approach.[4,5] For example, the meta-analysis of Berghaus et al[6] 2011, on the clinical relevance of the effects of psychotropic substances on driving and driving-related psychological functions, referred to a meta-analysis of 450 studies on alcohol-related deficits.[7] The International Council on Alcohol, Drugs, and Traffic Safety (ICADTS)[8] grouped medical drugs into 3 categories. Each of those categories is related to the effects of benchmark BACs as follows:

1. Presumed to be safe or unlikely to produce an effect (equivalent to a BAC that is less than 0.05%).
2. Likely to produce minor or moderate adverse effects (equivalent to a BAC between 0.05% and 0.08%).
3. Likely to produce severe adverse effects or presumed to be potentially dangerous (equivalent to a BAC that is more than 0.08%).

Levels of 0.05% and 0.08% BACs are considered meaningful benchmarks because 0.05% BAC is the legal limit in most of the countries in the European Union and 0.08% BAC is the legal limit in the United States. Epidemiological data on the correlation between BAC and accident risk[9,10] revealed that the accident risk increases from a BAC of 0.04% and exponentially rises from 0.10%.

Pioneer work on the alcohol-calibrated assessment of drugged driving was done by a work group at the Maastricht University in the Netherlands.[11] Louwerens et al[12] tested 24 social drinkers using the Highway Driving Test under placebo and with 0.03%, 0.06%, 0.09%, and 0.12% BACs in a partially blind crossover design. The subjects drove a specially instrumented car on a highway circuit and had to maintain a constant speed and steady lateral position. The primary endpoint was the standard deviation of lane position (SDLP), an indicator of lane-keeping performance. The researchers found that the SDLP increased exponentially with a rising BAC. Thus far, these alcohol data have served as a comparison in more than 75 studies that assessed drug-induced deficits by the Highway Driving Test.

However, because the Highway Driving Test puts a major focus on the SDLP, the operational level of driving is primarily considered and the cognitive or higher levels of driving[13] are disregarded. To measure sedative effects of a certain drug, the SDLP is a very sensitive parameter. However, lane-keeping performance does not take into account factors such as situation perception or risk awareness, which may be especially impaired by, for example, stimulating drugs. Hence, the Car Following and

From the *Würzburg Institute for Traffic Sciences (WIVW), Veitshöchheim; and †Department of Psychology, Center for Traffic Sciences, University of Würzburg, Würzburg, Germany.

Received April 8, 2014; accepted after revision December 29, 2014.

Reprints: Yvonne Kaussner, PhD, Würzburg Institute for Traffic Sciences, Robert-Bosch-Str. 4, 97209 Veitshöchheim, Germany (e-mail: yvonne.kaussner@wivw.de).

The authors are completely responsible for the scientific content of this article.

‡Hans-Peter Krüger, PhD, is deceased.

ISSN: 0271-0749
DOI: 10.1097/JCP.0000000000000285

City Driving Test were developed to assess longitudinal control and higher demands of attention in real traffic at the tactical level.[14–16] Ideally, studies should include the Highway Driving Test as well as the Car Following Test and the City Driving Test to study driving performance as a whole. However, this would be time consuming and very difficult to realize. Furthermore, tactical and higher cognitive aspects of driving can hardly be standardized in real traffic because it is often difficult to control external factors, such as surrounding traffic or weather conditions.[15]

Modern driving simulators are an interesting alternative to classic on-road tests because they allow the operational and tactical levels of driving to be immediately tested in a standardized, reproducible, and safe way. To the best of our knowledge, there have been 2 alcohol calibration studies done in driving simulators that explicitly investigate the effects of alcohol on different levels of driving.[17,18] Veldstra et al[17] performed an alcohol calibration study of a test course that included various scenarios and driving tasks in a fixed-base driving simulator. Seventeen drivers were tested under 0.03%, 0.05%, and 0.08% BACs. However, in this crossover design, many of the scenarios (especially those requiring reactions to unexpected events) were vulnerable to practice effects; this, in turn, may have interfered with potential alcohol-induced deficits. Thus, SDLP was the only sensitive outcome parameter. Berthélon and Gineyt[18] investigated the influence of 0.00%, 0.03%, 0.05%, and 0.08% BACs on speed behavior, lane-keeping performance, and reaction to sudden events. They found increasing performance decrement with increasing BAC for lane-keeping performance and speeding behavior but no effect for reaction times. Especially for the urban scenarios, no effects of alcohol were found, which again might be—according to the authors—due to practice effects. Furthermore, the authors argued that the weak sensitivity of the urban scenarios may be partly linked to the high variability of possible avoidance strategies to the sudden events (braking, drawing aside, and varying approaching speed). One solution for this might be not only to take a single parameter into account to evaluate the situation (ie, reaction time) but also to rate different aspects of the situation (eg, speed behavior, lane keeping, securing behavior, distance to other cars, adherence to traffic rules) and then to aggregate those ratings afterward to one global measure of driving performance (eg, total number of errors).

At the Würzburg Institute for Traffic Sciences (WIVW), we developed a representative test course that can be used to test operational and tactical aspects of driving in a safe and reliable manner. This test course meets all of the requirements for on-road driving tests in real traffic according to the relevant literature, various guidelines, and traffic-psychological classifications of driving.[13,19,20] It consists of representative, moderately difficult scenarios on rural roads, on highways, and in urban traffic. In addition, a monotonous nighttime section was added, which had proven to be specifically sensitive to daytime-sleepiness and sedating medicines in prior studies.[21,22] Scenarios that require reactions to sudden events or mistakes of other road users were avoided because they are often prone to practice effects as previously described and observed during the development of test courses for our own studies.[21,22] As suggested above, various driving performance parameters reflecting different aspects of driving were measured and then aggregated to a global measure of driving performance.

The objectives of the present study were to collect alcohol calibration data (0.00%, 0.05%, and 0.08% BACs) for this representative test course to validate it and to assess the clinical relevance of findings in future clinical studies using the same experimental setup.

On the basis of the findings of the meta-analysis from Schnabel et al,[7] we hypothesized that the effects of alcohol depend not only on the type but also on the level of difficulty that the applied test scenario has as well as on the driving performance parameter in question. We expected that all aspects of driving deteriorate with increasing levels of alcohol but that the operational aspect of driving (particularly lane keeping) is more affected than the cognitive aspect.

METHODS

Overview

This double-blind, randomized, crossover study investigated the effects of 0.00%, 0.05%, and 0.08% BACs on driving performance in a randomized and counterbalanced order. To evaluate driving performance globally, various parameters of different data sources were considered as follows:

1. Expert global assessment on a rating scale of fitness to drive.[23]
2. Number of driving errors registered and classified according to Kaussner et al.[22]
3. Well-established tactical and operational driving parameters recorded by the simulation software.
4. Subjective assessment of driving performance on the rating scale of fitness to drive.

The study was carried out in accordance with the World Medical Association's Declaration of Helsinki (Seoul Modification 2008) and approved by the medical ethics committee of the Bayerische Landesärztekammer (Bavarian Medical Association).

Subjects

Twenty-four subjects (11 women, 13 men) participated in the study. Appropriate test drivers were recruited from the test driver panel of the WIVW. Here, all test drivers have to complete a sophisticated simulator familiarization program by default. This is essential not only to help participants establish a more natural way of driving in the simulator but also to prevent simulator sickness.[3] The standard program includes at least 8 courses that last 10 to 25 minutes each; these courses are usually absolved in 2 sessions. For enrollment, subjects had to meet the following inclusion criteria: (1) healthy men and women aged 23 to 60 years; (2) valid driver's license; (3) the completion of the simulator familiarization program in the WIVW simulator with motion system[3] with "very good tolerance"; and (4) light to moderate alcohol consumption,[24] that is, not fewer than 1 alcoholic drink per month and not more than 14 drinks per week (1 drink corresponds to 12 g of alcohol).

Exclusion criteria were as follows: (1) acute or chronic illness; (2) continuous medicinal drug intake in the 14 days before the first test day up until the end of the study (exception: oral contraceptives); (3) any intake of medicinal drugs 48 hours before test days (exception: oral contraceptives); (4) consumption of alcohol, that is, a BAC of more than 0.00% at the beginning of a driving session; (5) more than 6 points in the Kurzfragebogen für Alkoholgefährdete (Short Questionnaire for Alcohol-Related Problems)[25]; and (6) only for women: positive pregnancy test and lactation. None of the enrolled subjects dropped out because of simulator sickness or for other reasons.

The subjects were instructed to get a good night's sleep the night before the test so that they are rested. Sleeping duration was controlled by a questionnaire at the start of each test day.

The mean age of the participants was 30 years (SD, 8.3; range, 23–53), and their mean body mass index was 24 (SD, 3.2; range, 20–32). They traveled a mean of 15,750 km per year by car (SD, 18,092; range, 2000–90,000). The mean Kurzfragebogen für Alkoholgefährdete score was 2.2 (SD, 1.5; range, 0–5).

Before participation, the subjects were given the opportunity to consult a physician from the Medizinisches Studienzentrum Würzburg, and written informed consent was obtained. Visiting

a physician was optional because only social drinkers who were familiar with the effects of alcohol in the applied dosages were included in this study. The subjects received 100 Euro for their participation.

A difference power calculation was performed. Thereby, we referred to a study investigating the impact of antiepileptic drugs in the same simulator with almost the same scenarios as in the present study.[22] In the monotonous nighttime scenario (which was also included in the present test course), SDLP was approximately 3 to 4 cm higher under carbamazepine (CBZ) as compared with a baseline without medication. Under both conditions, the SEM SDLP was 1 cm. Thus, the power calculation revealed that 24 subjects were sufficient for providing a power of 90% at a 2-sided level of 5% for detecting a mean difference of approximately 2 cm, which was considered as the lower limit for a clinically relevant deficit.

Treatment and Design

The influence of 0.05% and 0.08% BACs on driving performance was investigated by means of a double-blind, placebo-controlled crossover design. The participants did not know that there was a 0.00% condition; they were simply told that driving under the influence of different BACs would be investigated with a maximum target BAC of 0.08%. Furthermore, any personal contact between the subjects and the investigator assessing their driving performance was avoided. An assistant was responsible for preparing and administering the drinks, instructing the subjects, monitoring BACs, and presenting questionnaires. The investigators observed the subjects' driving behavior via monitors in a separate room (Fig. 1). To make the placebo condition more convincing, alcohol odors (tissue scented with vodka was hidden near the subjects) were diffused in the room where the drinks were given. Because of these arrangements, we think that the blinding worked quite well. This assumption was supported by subjective ratings of the test drivers; 11 of the 24 test drivers indicated that they were drunk in the placebo condition.

The participants were randomly assigned to 1 of $3 \times 2 \times 1 = 6$ possible treatment sequences. These sequences were recorded in a randomization scheme. Access to this scheme was restricted to the investigators' assistants who were responsible for preparing the drinks. At the screening, all eligible subjects were given a randomization number that assigned them to 1 of the treatment sequences. The subjects and the investigator remained blinded to the treatment sequence until database lock. Randomization data were kept strictly confidential until the time of unblinding.

Alcohol Application

The subjects were instructed to finish their last meal 4 hours before the test session. The required amount of alcohol needed to reach the target BAC was computed individually for each subject. The total body water of the subjects (TBW [milliliters]) was computed, with sex, weight (kilograms), and body height (centimeters) as variables in the following formulas[26]:

$$\text{For men: } TBW = 2.447 - (0.09516^{*}\,\text{age}) + (0.1074^{*}\,\text{body height}) + (0.3362^{*}\,\text{weight})$$

$$\text{For women: } TBW = 2.097 + (0.1069^{*}\,\text{body weight}) + (0.2466^{*}\,\text{weight})$$

To compute the required amount of alcohol needed for the target BAC, the product of the target BAC and the TBW was divided by the specific weight of alcohol (ie, 0.8 g/cm^3) and multiplied by a conversion factor of 1.3 (Vollrath, 2000, unpublished habilitation thesis, University of Würzburg). This factor served as correction for the light meal that the subjects received before consuming the drinks:

$$\text{Required alcohol quantum in gram} = BAC \times \frac{\text{TBW}}{0.8} \times 1.3$$

The driving test lasted approximately 1 hour, and the metabolization of alcohol begins immediately after the intake with a rate of 0.01% to 0.02% per hour. Therefore, a BAC value of 0.065% for the target BAC 0.05% and a BAC value of 0.95% for the target BAC 0.08% were inserted in the formula above.

The alcohol the subjects received was 37.5% vodka mixed with nonalcoholic, caffeine-free soft drinks (according to the preference of the subject). The total amount of 400 mL was subdivided into four 100-mL drinks. Each drink had to be drunk in 5 minutes. The BAC was measured 6 times with a breathalyzer (Alco-Testgerät 7410, Draeger).

Procedure

The subjects were recruited from the WIVW's test driver panel. Eligible subjects were invited by e-mail or telephone for screening. During the screening, the subjects' eligibility was reassessed, and thereafter, the subjects gave their informed consent. None of the subjects used the option to be advised by a physician.

The assessment of fitness to drive was carried out in 3 drinking sessions on 3 different days with an identical procedure. There were at least 3 days, but not more than 14 days between 2 test days. Each session started with a BAC test and, for the women, a pregnancy test. As mentioned above, the individual amount of alcohol was served in four 100-mL mixtures of vodka and a soft drink that had to be consumed in 5 minutes. Between the second and the third

FIGURE 1. The driving simulator of the Würzburg Institute of Traffic Sciences with motion system. The motion system (left) has 6 degrees of freedom. The visual system has 3 image channels that have a field of view of 60 degrees. The environment is also shown in the outside mirrors and the rearview mirror via liquid crystal display. The mock-up (middle) is a truncated BMW series 5. Simulation is operated from a separate room (right). During driving sessions, drivers, their behavior, and the simulated environment can be observed via several monitors (on the right side) and driving errors can be registered without disturbing the driver.

drink, the participants drove 10 minutes in the driving simulator to refamiliarize themselves with it. In total, BAC was measured 6 times: once before the first drink, once after the familiarization drive, and before and after each of the 2 parts of the actual test drive. During the test drives, a specially trained investigator registered the subjects' driving errors. After the last part of the test course, both the investigator and the subjects themselves rated the driving performance on the Fitness-to-Drive Scale.

Driving Simulator Test

Driving performance was measured in the WIVW's motion-based driving simulator that runs with the software SILAB (Fig. 1). At the WIVW, this simulator is used to conduct clinical studies that investigate the effects of medicinal drugs on driver fitness. The software SILAB and various configuration stages of the simulator are commercially available (WIVW, Veitshoechheim, Germany, www.wivw.de).

The test course was designed to assess safe driving in compliance with the German Traffic Regulations[27] while considering both the tactical and operational levels of driving.[13] The course consisted of a representative range of scenarios from the scenario package "Driver Fitness and Ability" (SPDE_DFA) included in the simulation software, SILAB (version 3.0). The subjects were instructed to drive safely, accurately, and quickly without violating the rules of the road. Furthermore, they were told to follow the directions indicated by a simple navigation system (arrows shown on an liquid crystal display on the center console).

Most of the scenarios had already been used and proven to be sensitive to neurological diseases and psychoactive drugs in other clinical studies.[21,22] To ensure representativity, care was taken that all driving tasks listed in the guidelines of the ICADTS[20] were included and that all categories of driving errors[19] could occur repeatedly. The test course was roughly 80-km long and could be driven in approximately 60 minutes.

Time of alcohol consumption and testing was held constant between and within subjects. Drinking always started at 3:00 PM (±30 minutes); the first part of the driving test started 45 minutes afterward.

Detailed Description of the Test Course

The test course was designed in 3 parallel versions as described elsewhere[22] and contained sections on rural roads with crosstowns, on highways, and in urban traffic (Fig. 2). The 3 highway sections specifically addressed the tactical level of driving and higher cognitive aspects (performing lane changes, dealing with the communication of other vehicles, etc). The urban scenarios also addressed higher cognitive aspects of driving (eg, intersections of varying complexity and rules of priority).

Several rural road scenarios required driving maneuvers that primarily focused on tactical aspects, such as speed adaptation and rules of priority (eg, sharp left/right turns, tunnel). Two scenarios specifically addressed rules of priority and gap acceptance:

- "Passing a breakdown van/rock fragments" with oncoming traffic: To pass these obstacles, drivers have to change to the left lane while observing oncoming vehicles. Time gaps between oncoming vehicles (longitudinal gaps) increase by 1 second, with the first gap lasting 11 seconds and the last gap lasting 14 seconds.
- "Crossroads with a stop sign/yield sign": Drivers have to drive straight through the intersection and have to choose an appropriate time gap between vehicles approaching from the right (lateral gaps) increasing by 1 second, with the first gap being 2 seconds and the last gap being 11 seconds.

Various tracking scenarios in rural sections with varying degrees of difficulty were included. The so-called vigilance section is a monotonous and relatively easy tracking task done at (simulated) nighttime to assess vigilance.[7] It is 24-km long and takes place on a rural road. Another vehicle is driving ahead with a speed of approximately 90 km/h, no passing is allowed, and there are no intersections. Lanes have a width of 3.50 m; straight sections (500 m) are alternated with smooth right and left curves that are 500-m long and have a curvature of 1/800 m and 1/200 m. In prior studies,[21,22] this scenario proved to be particularly sensitive to sleepiness and sedation.

The "simple route following" is an easy tracking scenario that is 2-km long. This scenario is best used to assess alertness.[7] It takes place on a rural road with alternating straight sections, 2 right curves and 2 left curves, each with a length of 450 m and a low curvature of 1/800 m.

The "winding timbered road" is a relatively difficult lane-keeping task on rural road that is 5-km long and best used to assess sustained attention.[7] This scenario is prone to lane departures due to summits and dips, curves that permanently vary between 1/77 m

FIGURE 2. Examples for operational (upper row from left to right: vigilance section, winding timbered road) and tactical scenarios (lower row from left to right: lane changes on highway, intersection in town).

and 1/1229 m, a restricted lane width of 2.75 m, and the vision-restricting planting. The speed limit is 80 km/h. There is oncoming traffic, but no traffic ahead.

Assessment of Driving Fitness

As a global measure of driving fitness, a specially trained investigator assessed the driving behavior using the Fitness-to-Drive Scale.[23] This scale has 3 verbal categories (driving behavior is normal, driving behavior is impaired, and driving behavior is critical). Each of these categories is subdivided into 3 numerical subcategories that allow for a more differentiated staging of driving fitness. At the upper and the lower end, the scale is complemented by the extreme categories "absolutely unfit to drive" and "fit to drive without any restrictions." On the scale, the subjects' driving performance was rated separately for each of the scenarios and for the course as a whole. In appropriate rater trainings, the 4 investigators registering driving errors in this study reached an interrater reliability between 0.833 and 0.944. After the drive, the subjects rated their own driving performance using this scale.

Driving errors were registered according to Kaussner et al.[22] This classification was based on a review of relevant literature.[19] The total number of driving errors and the following subcategories of errors were analyzed:

1. Tactical errors with respect to longitudinal control (speed too high, too low, inadequate speed/acceleration/deceleration, time headway (THW) too low/tailgating).
2. Operational errors with respect to lateral control (bad lane keeping/lane departures, lateral distance to objects/vehicles too low).
3. Cognitively based tactical errors (violating right of way, delayed securing, overcautious securing, errors in changing/choosing lanes, driving on impermissible lanes, no/untimely blinking, no/ambiguous/inappropriate dealing with communication with/of other road users, navigation errors).
4. Collisions and critical situations.

Lateral position, headway to other vehicles, and speed were continuously recorded with a sampling rate of 100 Hz by means of the driving simulation software. For the "simple route following," the "winding timbered road," and the "vigilance section" tracking scenarios, data were separately reduced to the following well-established endpoints:

- Lateral control (operational level): SDLP (meters) and number of lane departures. SDLP was calculated according to Verster and Roth,[28] with lane departures being excluded to avoid an overestimation due to outliers.
- Longitudinal control in the vigilance section with a leading vehicle (tactical level): percentage of time tailgating (THW < 1 second).
- Longitudinal control in the simple and difficult tracking scenarios in which speed was not restricted by a leading vehicle (tactical level): mean speed (kilometers per hour).

The number of lane changes and the percentage of time on the left lane during driving on the highway as well as the size of accepted gaps at intersections and while passing obstacles were registered as additional tactical parameters.

Statistical Analysis

Repeated-measures analyses of variance (ANOVAs), with the within-factor BAC (0.00%, 0.05%, and 0.08%), were computed. If ANOVAs were not adequate (eg, because of skewed distributions), nonparametric Friedman ANOVAs were carried out. Analyses of variance on percentages (percentage of time tailgating, percentage of time on the left lane) were performed after a logit transformation $\ln(p/(1-p))$.

Significant effects were followed up by comparisons of means (*t* tests). A significance level of 5% (2 sided) was set for all analyses. To control for an alpha-inflation, a hierarchical test procedure[29] was applied that tested parameters deductively.

The analyses were performed by means of the computer software, IBM SPSS Statistics for Windows (version 19.0).

RESULTS

Blood Alcohol Concentration

In the 0.05% condition, the subjects started to drive with a mean BAC of 0.058% (SD, 0.02%) and finished with a mean BAC of 0.044% (SD, 0.01%). In the 0.08% condition, the subjects started to drive with a mean BAC of 0.079% (SD, 0.02%) and finished with a mean BAC of 0.077% (SD, 0.01%). In the placebo condition, BAC was 0.00% during the entire test period.

Driving Performance

All results of the ANOVAs from the investigators' assessments, subjective ratings, and driving parameters are summarized in Table 1. Throughout all of the significant effects, we computed the corresponding effect sizes that reached values greater than 0.14 (η^2) respectively 0.8 (Cohen *d*). According to the benchmarks suggested by Cohen,[30] these effect sizes can be interpreted as large.

As reflected in the driving fitness ratings for the total test course, the blind investigators assessed the subjects' driving performance as normal when they drove under placebo (mean, 2.9; SD, 1.1). Under alcohol, the driving fitness ratings of the investigators reached the level of a mildly impaired performance; ratings under 0.05% BAC (mean, 3.6; SD, 1.5) differed only by trend ($P = 0.061$) and ratings under 0.08% BAC (mean, 3.8; SD, 1.6) differed significantly ($P = 0.005$) from the placebo condition. No significant difference between the ratings under 0.05% and 0.08% BAC could be proven ($P = 0.554$). The subjects rated their alcohol-induced deficits slightly more severe than did the investigators. Their ratings were significantly worse under the influence of alcohol than under placebo (mean, 2.7; SD, 2.3), but there was no significant difference between 0.05% (mean, 4.5; SD, 2.0) and 0.08% BAC (mean, 4.8; SD, 2.0).

The total number of driving errors differentiated between all BAC conditions. All of the post hoc comparisons were significant, indicating that the number of driving errors was lowest under the placebo (mean, 50.2; SD, 21.4), medium under 0.05% BAC (mean, 71.6; SD, 37.5), and highest under 0.08% BAC (mean, 86.2; SD, 50.3). Subdividing driving errors in categories (ie, lateral control, longitudinal control, and cognitive errors), the difference between the placebo and alcohol conditions was significant for all categories, but the difference between 0.05% and 0.08% (although descriptively existent) revealed a tendency for longitudinal errors only. The number of critical situations and collisions was the only parameter that did not increase significantly under alcohol.

Lateral driving parameters differed distinctly depending on the underlying scenario: For the simple and monotonous scenarios, the SDLP was sensitive, whereas for the difficult scenario, the number of lane departures as an indicator of very poor tracking differentiated between the placebo and alcohol conditions.

At large, the operational lane-keeping parameters SDLP and number of lane departures were more sensitive to the alcohol

TABLE 1. Summary of Results

	Mean (SD)			ANOVA
	0.00%	0.05%	0.08%	F (P)/χ^2 (P)
Global assessments and driving errors				
Expert Fitness-to-Drive ratings	2.9 (1.1)	3.6 (1.5)	3.8 (1.6)	**3.9 (0.029)*,(a),b**
Subjective Fitness-to-Drive ratings	2.7 (2.3)	4.5 (2.0)	4.8 (2.0)	**16.8 (0.000)*,a,b**
Total No. driving errors	50.2 (21.4)	71.6 (37.5)	86.2 (50.3)	**14.4 (0.000)*,a,b,c**
Errors in longitudinal control	24.1 (14.4)	30.9 (14.9)	37.2 (24.1)	**11.9 (0.000)*,a,b,(c)**
Errors in lateral control	20.1 (15.2)	32.1 (25.4)	38.7 (28.9)	**8.6 (0.002)*,a,b**
Cognitive errors	5.4 (2.4)	7.4 (3.7)	8.7 (4.6)	**6.6 (0.003)*,a,b**
Critical situations and collisions	0.7 (0.7)	1.2 (1.9)	1.6 (2.9)	0.1 (0.958)†
Operational parameters				
Simple route following (SDLP), m	0.17 (0.04)	0.19 (0.06)	0.20 (0.05)	**4.3 (0.019)*,a,b**
Vigilance section (SDLP), m	0.20 (0.05)	0.23 (0.06)	0.25 (0.06)	**9.7 (0.000)‡,a,b**
Winding timbered road (SDLP), m	0.21 (0.03)	0.21 (0.05)	0.22 (0.03)	1.6 (0.220)*
Simple route following (LD), N	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	—
Vigilance section (LD), N	1.2 (2.8)	2.9 (6.8)	3.4 (6.3)	1.9 (0.162)‡
Winding timbered road (LD), N	2.9 (2.0)	6.4 (5.8)	6.7 (5.3)	**7.6 (0.000)*,a,b**
Tactical parameters				
Simple route following (mean velocity), km/h	100.7 (4.3)	100.8 (2.8)	101.9 (7.9)	0.7 (0.428)*
Winding timbered road (mean velocity), km/h	72.8 (5.1)	75.2 (5.6)	74.4 (4.7)	**4.1 (0.023)*,a,b**
Vigilance section (THW < 1 s), %	2.5 (6.8)	5.1 (9.2)	6.7 (9.6)	**7.4 (0.002)‡,§,a,b**
Lane changes on highway, N	22.3 (4.7)	22.4 (5.1)	24.3 (7.0)	**3.8 (0.029)*,b,c**
Time on left lane on highway, %	62.0 (7.2)	62.6 (7.1)	60.2 (8.7)	1.6 (0.219)*,§
Accepted longitudinal gaps (size), s	13.3 (0.8)	13.4 (0.9)	13.3 (0.8)	0.7 (0.699)†
Accepted lateral gaps (size), s	7.0 (1.9)	7.10 (2.1)	6.8 (2.2)	0.3 (0.751)*

For all analyzed parameters, the mean (SD) values are separately presented for placebo, 0.05%, and 0.08% BAC.

Bold data indicate significance of the $P < 0.05$ effect.

*ANOVA with 1 dependent factor (BAC).

†Nonparametric Friedman ANOVA.

‡ANOVA with 2 dependent factors (BAC, time).

§Analysis performed after logit transformation.

Post hoc tests revealed significant/(by trend) differences a/(a)between 0.00% and 0.05% BAC, b/(b)between 0.00% and 0.08% BAC, and c/(c)between 0.05% and 0.08% BAC.

LD indicates lane departure; N, number.

conditions than were the tactical and cognitive parameters recorded by the simulation. The most sensitive tactical parameter was the percentage of time following the leading vehicle, with a THW of less than 1 second in the vigilance section, indicating that tailgating was significantly more frequent under alcohol (P = 0.002). The subjects drove slightly faster under alcohol than under placebo only in the difficult tracking scenario (P = 0.023; mean, 75.2 km/h; SD, 5.6 for 0.05% BAC; mean, 74.4 km/h; SD, 4.7 for 0.08% BAC; mean, 72.8 km/h; SD, 5.1 for 0.00% BAC). This speed increase was accompanied by deficits in lane-keeping performance as described above. Under 0.08% BAC, the subjects changed lanes significantly more on highway sections (mean, 24.3; SD, 7.0) than when they were under placebo (mean, 22.3; SD, 4.7) and 0.05% BAC (mean, 22.4; SD, 5.1). Blood alcohol concentration did not affect the percentage of time driven in the left lane, nor did it affect the size of accepted gaps at intersections or while passing an obstacle.

DISCUSSION

The present study assessed the driving performance of 24 social drinkers under placebo, 0.05% BAC, and 0.08% BAC in a randomized, double-blind crossover design using a representative test course in a high-fidelity driving simulator. The aims of this study were to validate the experimental setup and to collect reference data for future clinical trials that focus on the impact of medicinal drugs on driving performance.

Overall, the blind investigators rated the subjects' driving performance as mildly impaired and as significantly worse under alcohol than under placebo. The same held true for the subjects' own Fitness-to-Drive ratings.

Generally, the results are well in line with the meta-analysis of Schnabel et al,[7] finding that tracking and psychomotor skills are already impaired by rather low BACs whereas cognitive functions are less affected. Also consistent with the relevant literature,[7,12,17,31,32] lane-keeping performance parameters were sensitive to the alcohol conditions. Findings regarding dose-dependent effects on SDLP for rather low BACs such as in the present study are mixed and not consistently proven in the literature.[12,17,31,32] In the present study, the difference between 0.05% and 0.08% BAC was not significant.

With respect to tactical parameters, the subjects not only drove slightly faster under the influence of alcohol in difficult tracking scenarios, but their tendency to tailgate was higher than

in the placebo condition. Additional tactical parameters, such as size of accepted gaps and percentage of time on the left highway lane, were not sensitive at all. This is in accordance with Veldstra et al,[17] who also found in their simulator study that there was no effect of BAC on the size of accepted gaps in BACs up to 0.08%. Maybe the investigated BACs were too low to detect significant effects with respect to such risky behaviors that were rather typical to higher BACs.[7]

As expected, parameters differed distinctly between the BAC conditions depending on the underlying scenario. This was especially obvious with the lane-keeping performance parameters: The SDLP clearly differed between alcohol and placebo in the simple and monotonous tracking scenarios but not in the difficult tracking scenario. This may be due to a ceiling effect in the difficult scenario. The number of lane departures was significantly heightened under alcohol in the difficult tracking scenario, whereas in easy tracking scenarios, no lane departure was observed at all. These findings are in line with a very recent study[33] that clearly showed that scenarios and driving performance parameters should be carefully selected so that their fit is optimal.

Simulators are a valid tool for assessing driving performance measures including speed, lateral position, and risky traffic behavior. Hereby, most of the measures fail to meet the requirements of absolute validity (ie, numerical accordance of a certain parameter between different simulators and on-road tests) because of differences in hardware, software, and scenarios. However, they do show relative validity (ie, the structure of the results between different simulators and on-road tests is the same), which is both necessary and sufficient for simulators to be a useful tool for studies on driving behavior (please refer to Mullen et al[34] for review). Keeping these limitations in mind, an isolated comparison of the mean SDLP changes to a placebo in the vigilance section of our study with those of other alcohol calibration studies performed on rather monotonous simulated and real tracks revealed to be quite similar: As in our study, other studies[12,17,31] found an increase of approximately 2 to 3 cm under 0.05% BAC and of approximately 4 to 6 cm under 0.08% BAC. Certainly, the alcohol-induced increase of the SDLP can be considered as reciprocal evidence for the (relative) validity of the experimental setting in all those studies.

For studies conducted in the WIVW driving simulator using identical scenarios, the data from the present study even allow for an absolute numerical comparison of pharmacological-induced impairments of driving performance with the effects of 0.05% and 0.08% BAC. For example, the impairment of driving performance under a subchronic influence of 600 mg of CBZ versus 900 mg of oxcarbazepine was tested in the WIVW driving simulator with a similar test course including an identical version of the vigilance section.[22] As compared with a baseline, SDLP increased by 1 cm under oxcarbazepine in the vigilance section. Under CBZ, SDLP increased by 3 cm—just as much as under 0.05% BAC in the present study. This fully corresponds to the data collected by Ramaekers et al.[35] In their study, they investigated the effect of a subchronic treatment with 600 mg of CBZ on SDLP by means of the Highway Driving Test. Standard deviation of lane position increased approximately 2 cm under CBZ and also under 0.05% BAC in the appropriate alcohol calibration study.[12] Consequently, both the present driving simulation test and the Highway Driving Test found CBZ to be comparable with a BAC of 0.05%. This can also be considered as evidence for the validity of our experimental setup as well.

Because there were no inclusion criteria for study enrollment regarding the annual mileage of the subject, there is a wide range of annual mileage between the subjects. Furthermore, there were no restrictions regarding caffeine and nicotine consumption; the subjects were just allowed to behave as they usually do. Finally, the subjects were not screened for psychoactive drugs. Admittedly, all of these points might have influenced the results. However, we assume that these factors did not vary significantly or systematically between the sessions so that these, for the most part, should have been controlled by the randomized crossover design.

In the present study, the investigators registering the driving errors were specially trained to ensure a high degree of standardization between the different investigators. After training, an interrater reliability between 0.833 and 0.944 was reached. This very high interrater reliability is possible because the scenarios and, more specifically, the behavior of other road users are highly standardized and raters are informed about the exact driving data that are presented on monitors by the driving simulation (Fig. 1); this also heightens objectivity.

As described above, most of the analyses revealed significant differences between the alcohol and placebo conditions, but the total number of errors was the only parameter discriminating significantly between all 3 BAC conditions. Because the alcohol-induced impairment of driving performance increases exponentially with rising BAC,[7,10] the considered BAC levels might have been too low to reflect significant dosage differences for the other parameters. Furthermore, longer test duration could increase the sensitivity of some parameters. This might be specifically true for the number of cognitive errors if a longer urban section would be added. With respect to the SDLP, we can refer to a prior study[22] in which the vigilance scenario was presented twice; this resulted in ceiling effects rather than to higher sensitivity. In the present study, we tried to do a trade-off with respect to the duration of the test course: Length was in accordance with the criteria on on-road tests to diagnose driver fitness of the relevant literature. Moreover, driving tasks according to various classifications were addressed by multiple scenarios, whereas test duration could be still tolerated well by the subjects.

That the total number of errors revealed to be the only parameter with a significant difference between 0.05% and 0.08% BAC might be furthermore due to the special characteristic of the representative driving course used in the present study: The test drivers could drive as they would in reality, and there are many degrees of freedom regarding the driving-related reactions to alcohol. For example, whereas one driver begins crawling along due to the sedating effects of alcohol, the next driver begins tailgating and speeding as a kind of alcohol-induced risk taking. Hence, both of these drivers make alcohol-induced mistakes, but the mistakes are different. Therefore, the total number of driving errors as an aggregation of all aspects of alcohol-induced impairments was more sensitive for different dosages of alcohol than were the single parameters.

In conclusion, for future clinical trials on drug-induced deficits of driving fitness, we recommend examining driving performance globally by a representative set of scenarios and a profile of various parameters addressing different levels of the driving task. On the basis of this performance profile, the total number of driving errors is recommended as the primary endpoint, as it revealed to be the most sensitive parameter because it could differentiate between the 2 alcohol dosages. Increases should be considered clinically relevant if they are equivalent to or higher than the effects of a BAC of 0.5 mg/mL; this is the legal limit for driving a car in most European countries. Subcategories of errors could be considered as secondary endpoints in an exploratory manner. In addition, an objective and specifically sensitive parameter chosen depending on the effect known to be induced by the tested drug should be considered. For example, the SDLP is a very reliable and sensitive parameter for sedative substances. In contrast to this, SDLP may be even ameliorated under the influence of stimulating

drugs.[36] For these drugs, driving parameters reflecting changes in the situation perception or risk awareness, such as speeding, tailgating, or violating right of way, might be more sensitive.

As shown in the present study, a representative set of driving scenarios in a driving simulator allows for the immediate testing of the operational and tactical levels of driving in a standardized, reproducible, and safe way and may therefore substitute classic on-road tests for clinical studies. The next step to further establish the representative driving course for clinical trials is a direct comparison of the performance on our simulated test course with the performance on a similar, real test course.

ACKNOWLEDGMENTS

The authors thank the staff of the Medizinisches Studienzentrum Würzburg for their assistance in consulting the ethics committee and their medical counseling as well as Julie Barthel, an American native speaker, for proofreading the paper.

Prof. Hans-Peter Krüger, PhD, died on October 24, 2012. We have lost an outstanding scientist and mentor. For the study presented in this paper, he contributed significantly to the development of the study design as well as to methodological issues, data analysis and interpretation.

AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

REFERENCES

1. Krüger H-P, Grein M, Kaussner Y. SILAB—a task-oriented driving simulation. Paper presented at: Driving Simulation Conference; November 30 to December 1, 2005; Orlando, FL.
2. Kaussner Y, Kenntner-Mabiala R, Hoffmann S, et al.Methodological issues on the impact of central nervous disorders or psychotropic drugs on driving performance: an alcohol reference study in driving simulation. Paper presented at: 9th Annual Scientific Meeting of the ISCTM; February 19 to 21, 2013; Washington, DC. Available at: https://isctm.org/public_access/Feb_2013/posters/Methdological_Issues.pdf Accessed December 15, 2014.
3. Hoffmann S, Buld S. Darstellung und Evaluation eines Trainings zum Fahren in der Fahrsimulation. In: VDI-Gesellschaft Fahrzeug- und Verkehrstechnik, ed. *Integrierte Sicherheit und Fahrerassistenzsysteme*. Düsseldorf, Germany: VDI-Verlag; 2006:113–132.
4. De Gier JJ, Alvarez FJ, Mercier-Guyon C, et al.Prescribing and dispensing guidelines for medical drugs affecting driving performance. In: Verster JC, Pandi-Perumal SR, Ramaekers JG, eds. *Drugs, Driving and Traffic Safety*. Basel, Switzerland: Birkhäuser; 2009:121–134.
5. Jongen S, Vuurman E, Ramaekers JG, et al.Alcohol calibration tests measuring skills related to car driving. *Psychopharmacology*. 2014;231:2435–2447.
6. Berghaus G, Sticht G, Grellner W. Meta-analysis of empirical studies concerning the effects of medicines and illegal drugs including pharmacokinetics on safe driving. October 18, 2011. Available at: http://www.druid-project.eu/Druid/EN/deliverales-list/downloads/Deliverable_1_1_2_B.pdf?__blob=publicationFile&v=1. Accessed October 7, 2014.
7. Schnabel E, Hargutt V, Krüger H-P. Meta-analysis of empirical studies concerning the effects of alcohol on safe driving. August 14, 2010. Available at: http://www.druid-project.eu/Druid/EN/deliverales-list/downloads/Deliverable_1_1_2.pdf?__blob=publicationFile&v=1. Accessed October 7, 2014.
8. The International Council on Alcohol, Drugs, and Traffic Safety (ICADTS). Appendix I—ICADTS drug list 2007. In: Verster JC, Pandi-Perumal SR, Ramaekers JG, eds. *Drugs, Driving and Traffic Safety*. Basel, Switzerland: Birkhäuser; 2009:519–540.
9. Borkenstein RF, Crowther FR, Shumate RP, et al.The role of the drinking driver in traffic accidents, the Grand Rapids Study. *Blutalkohol*. 1974;11:1–131.
10. Krüger H-P, Vollrath M. The alcohol-related accident risk in Germany: procedure, methods and results. *Accid Anal Prev*. 2003;932:1–9.
11. Vermeeren A, Leufkens TRM, Verster JC. Effects of anxiolytics on driving. In: Verster JC, Pandi-Perumal SR, Ramaekers JG, eds. *Drugs, driving and traffic safety*. Basel, Switzerland: Birkhäuser; 2009:289–305.
12. Louwerens JW, Gloerich ABM, de Vries G, et al.The relationship between drivers, blood alcohol concentration (BAC) and actual driving performance during high speed travel. In: Noordzij PC, Roszbach R, eds. *Alcohol Drugs Traffic Safety—T86*. Amsterdam, the Netherlands: Excerpta Medica; 1987:183–192.
13. Michon JA. A critical view of driver behavior models: what do we know, what should we do? In: Evans L, Schwing RC, eds. *Human Behavior and Traffic Safety*. New York, NY: Plenum Press; 1985:485–521.
14. Brookhuis KA. The role of traffic psychology in psychopharmacological research. *Transp Res Part F Traffic Psychol Behav*. 2014;25:120–126.
15. Owens K, Ramaekers JG. Drugs, driving, and models to measure driving impairment. In: Verster JC, Pandi-Perumal SR, Ramaekers JG, eds. *Drugs, Driving and Traffic Safety*. Basel, Switzerland: Birkhäuser; 2009:43–58.
16. Verster JC, Veldhuijzen DS, Patat A, et al.Hypnotics and driving safety: meta-analyses of randomized controlled trials applying the on-the-road driving test. *Curr Drug Safety*. 2006;1:63–71.
17. Veldstra JL, Brookhuis K, de Waard D. *Dose Related Effects of Alcohol on Simulated Driving Performance—A Calibration Study*. Groningen, the Netherlands: Report Department of Traffic and Environmental Psychology of the University of Groningen; 2010.
18. Berthélon C, Gineyt G. Effects of alcohol on automated and controlled driving performances. *Psychopharmacology*. 2014;231:2087–2095.
19. Brenner-Hartmann J. Durchführung standardisierter Fahrverhaltensbeobachtungen im Rahmen der medizinisch-psychologischen Untersuchung (MPU). Paper presented at: BDP-Kongress für Verkehrspsychologie; September 14, 2002; Regensburg, Germany. Available at: http://psydok.sulb.uni-saarland.de/volltexte/2006/741/pdf/brenner_01.pdf. Accessed December 15, 2007.
20. The International Council on Alcohol Drugs, and Traffic Safety (ICADTS). Appendix II—International Council on Alcohol, Drugs, and Traffic Safety. Guidelines on experimental studies undertaken to determine a medicinal drug's effect on driving or skills related to driving. In: Verster JC, Pandi-Perumal SR, Ramaekers JG, eds. *Drugs, Driving and Traffic Safety*. Basel, Switzerland: Birkhäuser; 2009:541–552.
21. Kaussner Y. Fahrtauglichkeit bei M. Parkinson [Driving ability in Parkinson's disease] [doctoral thesis]. May 7, 2007. Available at: http://opus.bibliothek.uni-wuerzburg.de/frontdoor/index/index/docId/1916. Accessed October 7, 2014.
22. Kaussner Y, Kenntner-Mabiala R, Hoffmann S, et al.Effects of oxcarbazepine and carbamazepine on driving ability: a double blind, randomized crossover trial with healthy volunteers. *Psychopharmacology*. 2010;210:53–63.
23. Neukum A, Krüger H-P. Fahrerreaktionen bei Lenksystemstörungen—Untersuchungsmethodik und Bewertungskriterien. In: VDI-Gesellschaft Fahrzeug- und Verkehrstechnik, ed. *Reifen-Fahrwerk-Fahrbahn*. Düsseldorf, Germany: VDI-Verlag; 2003;297–318.
24. Dawson DA, Grant BF, Chou PS. Gender differences in alcohol intake. In: Hunt WA, Zakhari S, eds. *Stress Gender and Alcohol-Seeking Behavior*. Bethesda, MD: NIH Pub; 1995:1–21.
25. Feuerlein W, Küfner H, Ringer CH, et al.Kurzfragebogen für Alkoholgefährdete (KFA). *Eur Arch Psychiatry Clin Neurosci*. 1976;222:139–152.
26. Watson PE, Watson R, Batt RD. Total body water volumes for adult males and females estimated from simple antropometric measurements. *Am J Clin Nutr*. 1980;33:27–39.

27. Schubert W, Wagner T. Die psychologische Fahrverhaltensbeobachtung—Grundlagen, Methodik und Anwendungsmöglichkeiten. *ZVS*. 2003;29: 119–127.

28. Verster JC, Roth T. Standard operation procedures for conducting the on-the-road driving test, and measurement of the standard deviation of lateral position (SDLP). *Int J Gen Med*. 2011;4: 359–371.

29. Marcus R, Peritz E, Gabriel KR. On closed testing procedures with special reference to ordered analysis of variance. *Biometrika*. 1976;63: 655–660.

30. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. Hillsdale, NJ: Erlbaum; 1988.

31. Mets MA, Kuipers E, Senerpont Domis LM, et al.Effects of alcohol on highway driving in the STISIM driving simulator. *Hum Psychopharmacol*. 2011;26:434–439.

32. Helland A, Jenssen GD, Lervag L-E, et al.Comparison of driving simulator performance with real driving after alcohol intake: a randomised, single blind, placebo-controlled, cross-over trial. *Accid Anal Prev*. 2013;53:9–16.

33. Zhang X, Zhao X, Du H, et al.Effect of different breath alcohol concentrations on driving performance in horizontal curves. *Accid Anal Prev*. 2014;72:401–410.

34. Mullen N, Charlton J, Devlin A, et al.Simulator validity: behaviors observed on the simulator and on the road. In: Fisher DL, Rizzo M, Caird JK, et al., eds. *Handbook of Driving Simulation for Engineering, Medicine, and Psychology*. Boca Raton, FL: CRC Press/Taylor and Francis Group; 2011:1–19.

35. Ramaekers JG, Lamers CTJ, Verhey F. A comparative study of the effects of carbamazepine and the NMDA receptor antagonist remacemide on road tracking and car following performance in actual traffic. *Psychopharmacology*. 2002;159:203–210.

36. Ramaekers JG. Effects of stimulant drugs on actual and simulated driving. March 1, 2011. Available at: http://www.druid-project.eu/Druid/EN/deliverales-list/downloads/Deliverable_1_2_1.pdf?__blob=publicationFile. Accessed December 15, 2014.