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Hangover Research Needs: Proceedings of the 5th Alcohol Hangover Research Group Meeting

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INTRODUCTION

Hangover is the most commonly reported negative consequence of heavy alcohol consumption. A large variety of symptoms have been reported the day after heavy drinking, which together are called the alcohol hangover. Frequently reported hangover symptoms include thirst, headache, drowsiness, and reduced alertness [1]. Although hangover is a common phenomenon in society and has serious socioeconomic consequences, it has received relatively little research attention. To increase research and international collaboration to examine the alcohol hangover, in 2010 the Alcohol Hangover Research Group (AHRG) was founded. This paper covers the research topics discussed at the 5th Alcohol Hangover Research Group meeting, held August 1–2, 2013 in Keele, UK.

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HANGOVER EFFECTS ON COGNITIVE FUNCTIONING AND DRIVING

The hangover state may impair cognitive performance which in turn may have a negative impact on daily activities such as driving a car and on-the-job performance. However, the currently available research often suffers from methodological shortcomings, differences in design which make direct comparisons difficult, and, as a result, inconclusive outcomes. Attention and memory appear to be broadly affected by alcohol hangover, but more research examining these effects in greater detail, together with executive functioning, is required [2]. It is also important to investigate to what extent performance impairment observed with cognitive tasks in clinical experiments translates to academic performance or real life activities such as driving a car. When designing hangover trials, it is important to take current research guidelines into account, by taking notice of the methodological issues discussed in the 2010 consensus paper of the Alcohol Hangover Research Group [3].

Lauren Owen (Keele University, UK) presented preliminary findings of hangover research funded by an EU Marie Curie Research Fellowship. In this on-going randomized, crossover trial, neurocognitive effects of alcohol hangover are examined in a sample of 200 students. Cognitive domains assessed include immediate and delayed declarative memory, working memory, attention and executive function, and mood. Participants are tested on 2 occasions following both an evening of alcohol consumption and abstinence. Preliminary analyses revealed significantly reduced feelings of alertness, contentment and a trend for reduced feelings of calmness during hangover. Alcohol hangover also resulted in impaired performance on working memory tasks as well as slower reaction times and greater number of errors, and impaired response inhibition. These findings support the existing literature that alcohol hangover affects cognitive and psychomotor functioning [2,4].

Since there are currently no effective hangover cures [5,6], it is likely that impaired cognitive and psychomotor functioning observed in experimental studies is reflected in daily activities. It is also likely that drinkers have to attend school or work the following day and thus risk that hangover affects their planned activities and performance. This has been confirmed by studies reporting on absenteeism and reduced productivity across various different groups of workers [7]. A recent study interviewing Dutch professional truck drivers revealed that in addition to causing significant socio-economic consequences, the alcohol hangover may also put those experiencing this post-intoxication state at increased traffic accident risk. This study showed that more than half of the professional drivers who consume alcohol and occasionally have hangovers report that they have driven while having a hangover during the past year, both private and professionally [8]. While most drivers admit to driving in the hangover state 'sometimes', about 10% of them state driving 'often' or 'always'. They acknowledge that during hangover their driving is impaired when compared to other (alcohol free) days. This study confirms that driving during hangover is a common phenomenon, and justifies further research to examine the impact of alcohol hangover on driving, and develop quick, on-road measurement methods of biomarkers of the alcohol hangover state.

Adriana Bervoets and Suzanne de Klerk (Utrecht University, The Netherlands) presented the results of a naturalistic study (using normal drinking episodes rather than experimental

dosing) examining the effects of alcohol hangover on simulated highway driving performance. Driving performance was tested the morning following an evening of consuming on average 10.2 alcoholic drinks (alcohol hangover) and on a control day (no alcohol consumed). In The Netherlands, a standard alcoholic drink contains 10 g alcohol. Social drinkers (N=42) performed a standardized 100-km highway driving test in the STISIM driving simulator [9]. It takes about 1 hour to complete the test. Standard Deviation of Lateral Position (SDLP, i.e. the weaving of the car) and lapses of attention were examined [10,11]. An explanation of SDLP measurement is given in Fig. (1).

A lapse was defined as a continuous change of lateral position of >100 cm for at least 8 seconds. Self-reported driving quality, driving style, mental effort, and sleepiness before and after driving, and hangover severity were assessed. SDLP (hangover – control) and lapses were related to the subjective outcome measures.

Driving performance was significantly impaired during alcohol hangover as expressed by a significant increase in SDLP and number of lapses relative to the control day, and significantly increased total lapse duration. The analyses further showed that during alcohol hangover, subjects reported that their driving quality was significantly poorer, and less safe, considerate, predictable, relaxed, and responsible. Also, significantly more effort was needed to perform the driving test during hangover. To illustrate the relevance of the magnitude of driving impairment during hangover it was compared to impairment observed in another study that tested the acute effects of alcohol using the same driving simulator test [9]. The effects on driving during hangover were greater than those seen with a BAC of 0.05 g%, i.e. the legal limit for driving a car in many countries. It was therefore concluded that highway driving is significantly impaired during alcohol hangover. Additional analyses revealed a significant moderating effect of total sleep time. This finding underlines the unique strength of a naturalistic design, in which these moderating factors become visible. In contrast, in controlled experiments, drinking time and sleep duration are usually controlled, masking their impact on next-day consequences of heavy alcohol consumption.

Chris Alford (University of the West of England, UK) examined the effects of alcohol hangover on a typical ‘commute’ or drive to work in a demanding driving environment, together with assessing subjective workload. Perceived workload has been largely ignored in relation to hangover, although Liu and Ho reported increased mental effort whilst driving under the influence of alcohol [12]. Thirteen female and six male drivers attended two experimental sessions, once the day following a night of drinking and once after no alcohol consumption in a counterbalanced design. They undertook a 20 minute drive in a mixed urban and rural environment with speed limit set to 50mph and hazards (e.g. pedestrians stepping into the road), as well as a divided attention task in the STISIM driving simulator. General impairment in the form of increased reaction time and SD speed (speed variability) were found during hangover when compared to the control condition, whilst more errors were seen with increased lateral position deviation, reflecting possible lapses. Even when knowingly impaired, participants can often maintain a good level of driving performance similar to an unimpaired state for a short time duration [13]. The current findings suggest that even shorter driving periods are detrimentally affected when in a demanding driving environment. The increased subjective workload reflects the increased effort participants

made in the hangover condition, but were unable to compensate for the resulting level of impairment.

The results of these two driving studies add to the growing body of evidence showing that alcohol hangover can significantly impair driving. Creating awareness of this problem may help reduce the total number of road traffic accidents which are predicted to become the fifth leading cause of deaths worldwide by 2030 [14].

HANGOVER SEVERITY, RESISTANCE, AND AGE

The presence of hangovers and their severity differ significantly between and within subjects, and previous research showed that there is a poor correlation between hangover severity, total alcohol consumption, and (estimated) BAC [15,16].

There is debate about the BAC level that should be reached to provoke a hangover. Previously, it was suggested that a peak BAC of at least 0.10 g% should be reached to provoke a hangover [17]. As a result, study participants that do not reach this BAC are typically excluded from further analysis. It can be questioned if this is correct. First, the peak BAC of 0.10 g% is not supported by scientific research, but based on consensus and the usual permissible limit in experimental dosing studies. Human subjects concerns commonly restrict the dose of alcohol consumed in experiments to BACs of only about 0.10%, while “normal” binge drinking occasions may result in BACs two or three times this level.

Second, it can be argued that everybody who reports a hangover should be included in the analysis. Alternatively, a peak BAC corresponding to drinking to intoxication (e.g. 0.05 g% or 0.08 g%) could be used as cut-off to define having a hangover. However, several naturalistic studies and surveys reveal that people who do not achieve a peak BAC of 0.10 g% or 0.08 g% also report having a hangover and suffer from a variety of hangover symptoms [1]. Excluding these participants from statistical analyses does not seem warranted. Future analysis of combined large datasets should determine if a peak BAC cut-off value is necessary to provoke a hangover, or whether every drinker who reports a hangover should be included in the analyses irrespective of their peak BAC. It is also not clear if it is the peak BAC that is important or the total dose of alcohol (which if consumed over a period of time may not result in really high BACs).

Darren Kruisselbrink (Acadia University, Canada) examined the proportion of students who report not experiencing a hangover, the frequency distribution of students across each rating score of the Acute Hangover Scale (AHS) single-item hangover question [18], as well as estimated BAC distribution quartiles for each hangover severity rating score. Students who rated their hangover after their heaviest drinking episode as ‘absent’ and who also did not indicate experiencing a hangover in the past month were considered ‘hangover immune’ (HOI); those who indicated experiencing a hangover in the past month, but not following their heaviest drinking episode were considered ‘hangover resistant’ (HOR). For those claiming hangover immunity, the majority of their BAC’s (~75%) clustered below a BAC of 0.10 g%. Comparing different peak BAC groupings revealed that with increasing peak BAC the percentage of people who claim not to have a hangover decreases dramatically. The data

from Acadia University show that for a substantial number of subjects total alcohol consumption in real life leads to a BAC greater than 0.10 g%, but within this group, the number of hangover immune drinkers seems much smaller than the percentage of 23% found in experimental studies with peak BAC levels around 0.10 g% [19].

Richard Stephens (Keele University, UK) discussed the results of age differences on experiencing a hangover. Examining a Danish dataset of over 50,000 adults revealed that experiencing hangover after binge drinking is much more common in young adults compared to older adults [20]. Unfortunately, the dataset provided no information on the total amount of alcohol consumed that resulted in a hangover. Previous research has shown that the amount of alcohol consumed during binge drinking episodes reduces across the adult age span [21]. In this study, a reduction of about one third was seen in alcohol consumption of elderly (65+ years) when compared to those aged 18–24 years old. The latter may explain the finding of the reduced incidence of having hangovers in the elderly. Hence, more research is needed to confirm if there is an actual reduction in sensitivity to having hangovers in the elderly, or if they are simply consuming less alcohol while binge drinking and therefore have less hangovers.

STATISTICAL AND METHODOLOGICAL CONSIDERATIONS OF HANGOVER RESEARCH

Response times (RTs)—the time elapsing between the appearance of experimental stimuli and the execution of an overt response from participants—are a popular and powerful measure for assessing cognitive functioning. As such, they are a promising avenue with which to explore putative effects of alcohol hangover on cognition. Typical RT analysis examines group/condition differences on measures of central tendency, typically the arithmetic *mean*.

In his presentation, James A. Grange (Keele University, UK) discussed some limitations of examining mean RTs. It was argued that when only looking at means, a lot of important information is simply ignored. In addition, differences between means—if found—provide limited insight, as RTs are not a measure of a unitary process. Also, true differences in groups can become null at the mean level. This latter point is important for hangover research, as group differences for RT are often negligible.

To illustrate some limitations of looking simply at mean RTs, Fig. (2) summarizes hypothetical data from an RT experiment collected during hangover and a control day.

Statistical analysis comparing the average RT reveals no significant difference between the hangover and control conditions, as the mean is 700 milliseconds for both. However, there are clear group differences at the level of the RT distribution between conditions, with hangover condition producing more variable responding, which goes unnoticed when only comparing the means with a traditional paired-samples t-test.

Two recommendations for researchers to examine and statistically analyze RT data were discussed. First, analysis of group differences across whole-RT distributions was suggested,

which requires estimating parameters for a mathematical function that fits the shape of RT distributions (specifically, the ex-Gaussian distribution). The resulting parameter estimates describe the shape and spread of RT distributions for each participant, and as such are more sensitive to potential group differences at the distribution level. Secondly, fitting computational/process models to RT data was recommended. Process models have parameters that reflect psychologically meaningful processes. For example, the Ratcliff Diffusion model of RT data allows the researcher to estimate the potential impact of alcohol hangover on several important RT processes: *drift rate*, which reflects the strength of evidence accumulation towards the correct response during response decision; *response boundary*, which reflects how much evidence is required before a response is executed (a higher response boundary parameter estimate reflects a more cautious responder, leading to slow but accurate responses); and *non-decisional processes*, such as perceptual encoding of the stimulus and time for motor responses. Examination of the potential effects of hangover on these different parameters provides researchers with a more sensitive, and more psychologically informative, examination of RT data.

BIOMARKERS OF THE ALCOHOL HANGOVER STATE

Alcohol biomarkers have a potential role in providing an objective measure of alcohol consumption in alcohol hangover research studies. This is desirable for a number of reasons – it can counter recall issues of the participants in terms of how much alcohol they have consumed, it can prevent bias by allowing naturalistic studies to be designed where the role of alcohol consumption is not overtly stated. Kate Jones (Health & Safety Laboratory, Buxton, UK) and Gordon Smith (University of Maryland, USA) discussed potential biomarkers of the alcohol hangover state, and methodological issues in collecting and storing blood, urine and saliva samples.

There are a number of potential biomarkers arising from both the main and alternate pathways of ethanol metabolism - oxidative and non-oxidative direct biomarkers and products of tissue damage resulting from alcohol consumption. Ideally, biomarkers should correlate with the dose of alcohol, the severity of the hangover, and corresponding performance impairment.

Blood alcohol concentration (BAC) is an excellent biomarker of alcohol intoxication, and its relationship with performance impairment has been established. For example, there is a clear relationship between BAC and driving impairment [22] and the chances of having a traffic accident [23]. Unfortunately, BAC is not a useful biomarker of alcohol hangover, since hangovers develop the following day after an evening of drinking when BAC recordings are usually zero. There are a number of indirect markers of tissue damage (e.g. liver function tests such as GGT, AST, ALT), mean corpuscular volume(MCV), and carbohydrate deficient transferrin (CDT)), that are indicators of heavy alcohol use. However these are generally long-term markers (requiring heavy alcohol consumption for at least two weeks before showing an effect) and several are non-specific [24]. Some, such as CDT, are sensitive and specific and may have a role in studies where long-term alcohol habits, or the effect of such habits on hangover propensity/symptoms, are being investigated. Direct, oxidative biomarkers of alcohol include acetic acid and acetaldehyde. Acetaldehyde has

been proposed as a relevant biomarker because it is responsible for many of the pathological effects of alcohol. Free acetaldehyde levels in blood are very rapidly eliminated (half-life less than 30 minutes) and so are therefore unsuitable. However, acetaldehyde can bind to proteins and so haemoglobin-bound acetaldehyde has been proposed as a long-term marker but due to the persistence (2–3 months) can only be used for assessing long-term alcohol habits (like CDT).

Several direct, non-oxidative, biomarkers of alcohol consumption are available including fatty acid ethyl esters (FAEE), phosphatidylethanol (PEth), ethyl glucuronide (EtG) and ethyl sulphate (EtS). All are sensitive and specific biomarkers of alcohol consumption although FAEE and PEth reflect chronic heavy drinking rather than short-term consumption [25]. EtG and EtS are complementary markers and are often measured together. They are short-term markers and are detectable for about 5 days after alcohol consumption. They are also measurable in a number of body fluids, including hair, meaning that longer-term consumption can also be assessed. Because of the high sensitivity, ‘unintentional’ exposures such as using alcoholic mouthwashes will be detectable. The value of a marker such as EtG is that its elimination reflects that of alcohol (peak excretion is about 3 hours after that of alcohol) and that it has limited inter-individual variation in metabolism due to factors such as age, gender, ethnicity – this allows a more reliable reconstruction of dose. Although EtG is widely reported in the scientific literature with regard to alcohol research, this is mostly focused on workplace alcohol testing and abstinence programs. Lewis *et al.* [26] reported that ethyl glucuronide can cause TLR4-dependent pain and that this could have implications for human conditions such as hangover headache. There are several studies underway examining the relationship of EtG concentration and hangover severity and to what extent EtG measurement is useful to predict performance impairment during alcohol hangover.

Jorinde Raasveld and Anna Hogewoning (Utrecht University, Netherlands) discussed the design of a new study to determine if people who claim to have no hangovers differ from those who do have hangovers after an evening of heavy alcohol consumption. To this extent, the two groups of social drinkers will be compared on cognitive performance measures during a hangover and control day (no alcohol consumed). In addition, urine and saliva samples will be taken to determine EtG and cytokine concentrations as biomarkers of the hangover state.

Two possible outcome scenarios of the study were discussed. First, the data may reveal that people who claim to have no hangover do not show performance decrement and no changes in EtG and cytokine concentrations. This would then suggest that these subjects are different from ‘normal’ drinkers in that they are not developing the unpleasant after effects of alcohol. Alternatively, the study may show that those who claim no hangover do show performance impairment and EtG and cytokine changes. This outcome would suggest that these subjects may not be aware of having a hangover. A possible reason for this lack of awareness may be that these subjects in general have a mental state comparable to the hangover state and therefore do not notice the difference with a hangover day.

DETERMINANTS OF HANGOVER SEVERITY

Besides total alcohol consumption, many factors may influence hangover severity. These factors may be genetic, psycho-social and personality differences between individual drinkers, but also include beverage type and their congener content.

Wendy Slutske (University of Missouri, USA) presented preliminary results from a study with the aims of examining: (1) sex differences in the occurrence of hangover, (2) the role of genetic factors in explaining individual differences in alcohol-related hangover, and (3) potential sex differences in the genetic contribution to hangover. Participants were drawn from a large interview survey of 4764 adult Australian twins. Analyses were restricted to the 94% of participants who had consumed alcohol in the past year. The focus was on four different hangover indices that have been previously described in the literature: frequency [27,28], severity [1], susceptibility [27,28], and insensitivity [19]. Frequency of hangover reflected the number of hangovers experienced in the past year. Severity of hangover was defined as the number of hangover symptoms that were experienced during the worst hangover suffered in the past year. Hangover susceptibility was quantified as the variance in hangover that remained after statistically controlling for the level of alcohol intake in the past year. Hangover insensitivity was defined as an individual who had been intoxicated at least once in the past year but had not experienced any hangovers (versus an individual who had been intoxicated and had experienced a hangover).

About half of the participants had experienced at least one hangover in the past year; the mean number of hangovers was six. There were differences between men and women in hangover frequency, but not severity, susceptibility, or insensitivity. There were important genetic contributions for all four indices of hangover, and this could not be completely explained by differences in the amount of alcohol consumed. This study provides much-needed evidence for important genetic underpinnings of individual differences in hangover, and provides novel insights into the etiologic structure of different hangover phenotypes.

Sam Royle (Keele University, UK) discussed psychosocial correlates of the alcohol hangover. Evidence for cultural, temporal and contextual differences in the effects and definitions of alcohol and alcohol related experiences [29,30] highlight the importance of non-biological factors in alcohol research. Relatively few studies have examined the relationships between alcohol hangover, mood, personality, and other psychosocial correlates such as guilt about drinking, however the small body of available evidence supports the idea of relationships between these variables [31,32]. There are issues to be contended with regarding previous research. Harburg *et al.*'s [31] work has become outdated, with more comprehensive, validated measures now available for measurement of mood, personality and guilt. Hesse [32] does not directly address issues of mood and personality in relation to alcohol hangover, but does relate a number of statements representing guilt and regret to the severity of alcohol hangover, however, this study was carried out with students on holiday, and as such may not represent a wider population, with drinking behavior changing while on holiday. Such evidence does however suggest that an understanding of the mood and personality effects in relation to alcohol hangover severity is required to account for individual variation in the phenomenon. To achieve this end, a

proposed naturalistic, correlational study was discussed, designed to look for correlations between measures of mood, personality, and guilt about drinking, with alcohol hangover severity.

Besides the total amount of alcohol consumed, it has been argued that congener content also has an impact on hangover severity. In addition to anecdotic evidence (i.e. high congener drinks such as tequila produce worse hangovers), some experimental studies confirmed that congener-rich beverages produce more severe hangovers [33]. Joris Verster (Utrecht University, The Netherlands) presented the results of a study that aimed to (1) develop a 'congener-index' of most commonly consumed beverages, and (2) examine how congener content and other factors relate to hangover severity. A survey was conducted among Dutch students examining their drinking behavior and latest alcohol hangover [1]. About half of the participants (n = 791) reported having had a hangover during the past month. For their last drinking session that resulted in a hangover, data was collected on the type and number of alcoholic and non-alcoholic beverages that were consumed. A literature search was conducted to determine the specific congener content of each beverage. The amount of carbohydrates, proteins, fats, ethanol, methanol, propanol-1, butanol-2, isobutanol, butanol-1, 2-methyl-butanol-1 and 3-methyl-butanol-1 was determined. Hangover severity was assessed with the Alcohol Hangover Severity Scale, AHSS [34], and a 1-item hangover score. The analyses showed that hangover severity scores correlated significantly with the amount of carbohydrates, proteins, fats, ethanol, and congeners. Regression analyses revealed that 12.6% of the variance of the AHSS could be explained by a model including 'ethanol amount', 'butanol-2 amount', 'monthly number of hangovers', 'number of cigarettes smoked', and 'gender'. Separate regression analyses were also performed for men and women. For women, 10.4% of the variance of the AHSS could be explained by 'ethanol amount', 'butanol-2 amount', and 'monthly number of hangovers'. For men, 16.3% of the variance of the AHSS could be explained by 'weekly alcohol consumption', 'butanol-1 amount', and 'number of cigarettes smoked'. The results confirm that many other factors besides total ethanol content contribute to hangover severity, including congener content, smoking, gender, weekly alcohol consumption, and previously experienced hangovers. Future research should examine these factors, using larger cohorts to also investigate potential gender differences.

DOES HANGOVER SEVERITY INFLUENCE TIME TO NEXT DRINK?

It has been suggested that having a hangover serves as a punishment for drinkers that will limit future alcohol consumption. Advocates of this hypothesis argue it is unwise to develop effective hangover cures since this may lead to increased alcohol consumption. There is however limited scientific evidence to support this hypothesis and other studies have shown that students do not adapt their drinking behavior despite having hangovers [35].

Prospective studies have established that frequent hangover [36] and an insensitivity to hangover after a challenge dose of alcohol [17] in young adulthood forecast problematic alcohol involvement and alcohol use disorder (AUD) diagnoses years later. To better understand these effects, investigations of the influence of hangover events on near-term drinking behaviors are needed. One possibility is that hangover could accelerate drinking if

sufferers pursue “hair of the dog” drinking to alleviate hangover symptoms [37,38]. This might explain why frequent hangover would forecast later AUD. A second possibility is that hangovers serve to punish heavy drinking, delaying or constraining future alcohol use [27,38]. If this is the case, drinkers who are insensitive to hangover effects might be at risk because they lack this inhibitory mechanism. In this scenario, the association between frequent hangover and AUD could be a marker of a distinct risk process, such as deficiency in the ability to learn from punishment.

To explore these questions, Thomas Piasecki (University of Missouri, USA) conducted survival analyses using data from 386 frequent drinkers who participated in a 21-day Ecological Momentary Assessment investigation. The analyses involved 2,276 index drinking episodes, of which 463 (20%) were followed by hangover. Results revealed modest and inconsistent effects of hangover events on time to the next drink. It is possible that hangover truly has little impact on drinking decisions or that the absence of strong effects arises because hangover has heterogeneous effects across drinkers. An important caveat is that the findings were obtained in a naturalistic study and thus examined the impact of hangovers among individuals who actually experience them in daily life. Individuals who find hangovers punishing may regulate consumption, avoiding hangovers, and therefore not contributing information to the modeled risk set. Additionally, the analyses did not address whether hangover influences other important aspects of drinking, such as the amount of alcohol consumed in subsequent sessions. If hangovers do not modulate near-term drinking, how should we understand the prospective associations between hangover measures and later alcohol problems? One possibility is that hangover measures are markers of a broader underlying risk process. This idea is supported by recently published findings from the same sample documenting that a low sensitivity to acute alcohol effects is associated with both frequent hangover and hangover insensitivity [28].

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Learning Objectives

- Driving is significantly impaired during alcohol hangover
- Most people who claim hangover immunity do not achieve a BAC>0.10 g%
- EtG (ethyl glucuronide) is a promising biomarker of the alcohol hangover state
- Genetic differences are likely to be an important determinant of experiencing hangovers
- Congeners significantly increase hangover severity
- Having a hangover does not reliably speed or delay the time to the next drinking episode.

Future Research

- Further examine the genetic influences on alcohol hangover
- Research into psycho-social and personality correlates of the hangover
- Examine gender and age differences
- Research into hangover resistance and immunity
- Examine the effectiveness of biomarkers of the hangover state
- Explore the effects of hangover events on other aspects of subsequent drinking behavior, such as amount consumed or time to next binge drinking episode.

Fig. 1. Standard Deviation of Lateral Position (SDLP)

SDLP, the weaving index, is the standard deviation computed relative to the mean lateral position of the car over the entire 100-km drive. Higher SDLP values indicate less vehicle control, i.e. impaired driving.

Fig. 2. Hypothetical data from a reaction time experiment

The participant performed the test on a hangover and control day. The mean of both conditions is 700 milliseconds.