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Functional biomarkers for the acute effects of alcohol on the central nervous system in healthy volunteers

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The central nervous system (CNS) effects of acute alcohol administration have been frequently assessed. Such studies often use a wide range of methods to study each of these effects. Unfortunately, the sensitivity of these tests has not completely been ascertained. A literature search was performed to recognize the most useful tests (or biomarkers) for identifying the acute CNS effects of alcohol in healthy volunteers. All tests were grouped in clusters and functional domains. Afterwards, the effect of alcohol administration on these tests was scored as improvement, impairment or as no effect. Furthermore, dose–response relationships were established. A total number of 218 studies, describing 342 different tests (or test variants) were evaluated. Alcohol affected a wide range of CNS domains. Divided attention, focused attention, visuo-motor control and scales of feeling high and of subjective drug effects were identified as the most sensitive functional biomarkers for the acute CNS effects of alcohol. The large number of CNS tests that are used to determine the effects of alcohol interferes with the identification of the most sensitive ones and of drug–response relationships. Our results may be helpful in selecting rational biomarkers for studies investigating the acute CNS effects of alcohol or for future alcohol- interaction studies.

Introduction

Ethyl alcohol, or ethanol causes dose-dependent central nervous system (CNS) depression, which culminates in a state of general unconsciousness at high plasma concentrations [1]. Prior investigations indicate that the predominant mechanism of CNS depression involves selective alcohol interactions with ion channels that include allosteric enhancement of inhibition mediated by gamma-aminobutyric acid A (GABA-A) receptors, antagonism of excitation by N-methyl-D-aspartic acid (NMDA) glutamate receptors and possibly inhibition of central L-type Ca^{2+} channels [1, 2]. Although alcohol is classified as a sedative drug, it can also have stimulant effects [1, 3, 4]. The concentration- and time-dependence of its inhibitory and stimulatory properties in humans have not yet been fully elucidated, partly due to the complicated and variable pharmacokinetics of alcohol, but also to the lack of standarized tests for the CNS effects of ethanol.

Alcoholic beverages are used commonly and worldwide [5]. The CNS effects of acute alcohol administration have been frequently quantified and a wide range of methods are used in such studies to study the different effects of alcohol. The sensitivity of these tests to the effects of alcohol has often not been completely ascertained, and concentration– or dose–effect relationships have only rarely been systematically reported. An overview of the sensitivity and dose–responsiveness of different CNS tests to the effects of alcohol would be useful for future studies focusing on acute alcohol effects or drug–alcohol interaction studies, and would constitute a useful collection of tests to evaluate the acute effects of alcohol on the CNS.

A biomarker is described as a characteristic that is measured and evaluated as an indicator of normal or pathologic biological processes or pharmacologic responses to a therapeutic intervention [6]. A biomarker can be any response measure that shows a clear, consistent response to meaningful doses, across studies from a sufficient number of different research groups. A dose–response relationship and a plausible relationship between the biomarker and the pharmacology of alcohol provide

indications that a biomarker reflects pharmacological activity. Previously, these criteria were used to evaluate the usefulness of CNS-tests (or functional biomarkers) for the effects of antipsychotic drugs [7], benzodiazepines [8], selective serotonin re-uptake inhibitors (SSRIs) [9], 3,4-methyleendioxymethamfetamine (MDMA) [10] and Δ^9-tetrahydrocannabinol (THC) [11] in healthy subjects. In general, these systematic reviews showed that only a small number of tests actually display proper characteristics for a meaningful effect biomarker, that these tests differ between the various drug classes, and that most of these biomarkers belong to a small number of functional CNS-domains: attention, memory, visuomotor and motor performance, subjective effects and certain neurophysiological tests (eye movements, electroencephalography). In addition, some drug classes cause specific neuroendocrine responses.

In an attempt to structure and subsequently evaluate the wide diversity of functional biomarkers for the CNS effects of ethanol, an extensive literature search was performed. Because of an apparent lack of standardization between the studies (even for the same tests), a structured procedure, described previously, was adopted, which includes progressive condensation of the tests into clusters of related tests and into domains of CNS functions, prior to the analyses [7–11]. The criteria mentioned for meaningful biomarkers were eventually applied to the results. All effects of alcohol other than on the CNS (e.g. on the liver) were excluded, except neuro-endocrine responses. The primary objective of the current review is to present a systematic overview of the usefulness of the different CNS tests described in the literature, which allow a reliable assessment of the acute CNS effects of alcohol in healthy adult volunteers. Accurate tests to measure the acute effect of alcohol on the CNS are vital when the effect of alcohol in combination with a CNS drug is being studied. The results of this review may also be useful to select rationally sensitive CNS test for drug–alcohol interaction studies, which are often required for registration of new CNS drugs.

Methods

Structured literature evaluation

'Ethanol' (MeSH), 'effect' and 'CNS' were used as pivotal keywords to construct a MedLine search. This search included a large number of studies that were irrelevant for the specific primary objective of this review. Therefore, a wide range of specific CNS functions was added to these keywords to ensure a comprehensive CNS effect profile. Subsequently, inappropriate terms (e.g. '*in vitro*', 'withdrawal' or 'deaths') were excluded from the search by using the '*NOT*' search option. To obtain a manageable data-set, the search was limited to 'adult: 19–44 years', 'English', 'publication date from 1980 to 2008' and 'humans'. The complete search query, which yielded 1263 publications, is provided in Table 1.

Table 1
Search query

Search query
(effect OR effects**) AND (**'ethanol'**[MeSH] NOT (patient OR patients OR genetic OR genetics OR disease OR diseases OR preclinical OR 'in vitro' OR death OR deaths OR traffic OR law OR laws OR injury OR injuries OR hangover OR withdrawal OR chronic OR sexual OR sexuality OR aggressive OR aggression OR MRI OR fMRI)) AND (**'central nervous system'**[MeSH] OR neurophysiology OR neuroendocrine OR neuropsychology OR subjective OR behaviour OR cognitive OR cognition OR performance OR executive OR attention OR visuomotor OR psychomotor OR motor OR memory OR sensory OR auditory OR visual OR language OR perception)** **limits: entry date from 1980 to 2008, humans, English, adult: 19–44 years**

All publications obtained using this strategy underwent a thorough selection process. Initially, all articles were manually screened by title. Articles with irrelevant titles, given the selected search terms were discarded. Remaining articles were carefully studied and those that did not comply with the main objectives of this review (e.g. studies describing chronic alcohol effects) were discarded. In addition, studies investigating alcohol effects under specific artificial circumstances or conditions (e.g. sleep restriction, hypoxemia or anxiety paradigms), and studies dealing with more drugs or substances than alcohol alone (i.e. interaction studies), were not selected for further analysis, even if part of the design complied with the requirements of this review. Also, studies investigating a specific group of subjects other than regular healthy adult volunteers (e.g. heavy drinkers, patients or certain professionals) were disregarded. Studies in which such populations were discussed have been excluded from our analysis, as in our opinion such populations exhibit different responses to similar doses of alcohol compared with 'healthy volunteers' and thus may negatively bias our results (e.g. pilots are supposed to have faster baseline reaction times in tests that measure reaction time speed and alcoholics probably show less effects in studies measuring subjective effects). Thereby, we only excluded tests that were also frequently reported in healthy volunteers (but with different results) rather than tests that were specifically used in these special populations. Furthermore, studies with fewer than 12 participating healthy volunteers were also disregarded. Finally, papers that only mentioned the dose of alcohol instead of the blood alcohol concentration (BAC) or the equivalent breath alcohol concentration (BrAC) were excluded, since these studies are less suitable for accurate analysis of the relationships between alcohol levels and effects.

Table 2
Criteria used for study evaluation

Evaluation criteria
Number of males
Number of females
Age (mean/range)
Blinding (open/single-blind/double-blind)
Randomization (randomized/non-randomized)
Design (parallel/cross-over)
Control (baseline controlled/placebo controlled)
Dose
Route (oral/intravenous)
BAC/BrAC
Test
Test item
Primary/secondary outcome parameter
Cluster
Domain
Effect (+/=/–)

At the end of this process, 218 titles were found eligible for review, which were subsequently evaluated based on the items summarized in Table 2. The results were captured into a Microsoft Excel® database. During this process the effect of alcohol on every individual test was scored, tests were grouped and alcohol concentrations were categorized.

Individual test results

Based on previous reviews [7–11], it was anticipated that in most cases no consistent quantitative results could be obtained from individual tests, because of the large diversity of methods, parameters and treatments. Therefore, the ability of a test to detect a statistically significant difference from placebo or baseline was scored as '+' (improvement/increase), '=' (no significant effect) or '–' (impairment/decrease). Subjective assessments of effects that were signs of improved CNS function or that most users would consider pleasurable (e.g. increase of a high or drug effect scale) were scored as an improvement/increase and symptoms of CNS depression or less desirable, adverse effects (e.g. increase of sedation or reduction of alertness) as an impairment/decrease. For physiological responses like changes in hormone concentrations or EEG power a functional interpretation was not always obvious, and these results were scored as increases (+), decreases (–) or as no change (=), according to the direction of the reported effects. The total numbers of (+) (–) and (=) were determined within each cluster and percentages were calculated. Afterwards, these percentages were visually inspected to detect whether alcohol mainly impaired, improved or had no effect on a certain cluster. Subsequently, the sensitivity of each domain to alcohol was evaluated by inspection of the number of clusters within a certain domain that was clearly affected by alcohol.

Some studies explicitly reported the use of several different tests in the methods section, without presentation of the results, for no apparent reason such as a separate publication. To avoid bias due to under-reporting of negative results, it was assumed that these tests had not shown any significant effects and were scored accordingly. In some studies with different drug doses, overall significances were reported for drug effects, without (*post hoc*) quantifications of the statistical significance levels for each individual dose. In these cases, efforts were made to estimate the individual dose effects from graphs or tables provided in the article. If this was impossible, only the largest average effect was assumed to be significant (in case of overall statistical significance) and smaller effects were considered non-significant.

Grouping of individual test results

Because of an apparent lack of standardization between the studies even for the same tests, a structured procedure was adopted as described previously [7–11] in order to obtain a meaningful overview. This approach allowed the preservation of individual study data in early stages, followed by a progressive condensation of results into logical test clusters and functional (CNS) domains. For example, all tests that determine the ability to discriminate flash- or flicker frequencies were grouped as the test cluster flicker discrimination and were subsequently categorized under the corresponding CNS domain attention. A compendium of neuropsychological tests from Spreen *et al.* [12] was primarily consulted to group functional tests into clusters of related tests or test variants. Additionally, the compendium of Lezak *et al.* [13] was frequently consulted. Occasionally, a specific test was not described in these compendia. In these cases, the authors' classification was followed or if necessary the test was clarified using other literature sources and classified by consensus. Tests and clusters were grouped further into domains that represent higher aggregates of integration of subjective, neuropsychological, neuroendocrine and neurophysiological functions. The neuropsychological domain is generally subdivided into executive functions, memory, attention, motor functions, language and perception [12]. For each test (or cluster), the compendia were also used to determine which CNS function was principally assessed by the test. Some tests provided different parameters with information on more than one functional domain. The results of the effects of a single test on different domains were scored separately, and the secondary effects were marked.

The effects of alcohol on multifactorial assessments like the Profiles of Mood States (POMS) [14], the Addiction Research Center Inventory (ARCI) [15] or the Bond & Lader visual analogue scales (VAS) [16] were frequently reported. Subscales of such inventories were grouped together if they fell in the same cluster. Sometimes, individual

subjective scales (and variants) were reported that could be regarded as variants from a basic form (e.g. subscales that are also part of more comprehensive tools like the Bond & Lader VAS). Such scales were clustered according to the original scale with which they corresponded (e.g. into scale alertness, scale mood or scale calmness in case of a Bond & Lader subscale). Within such clusters, all scales showing a significant effect were grouped, whereas all scales showing no effect were grouped separately. In this way, scales within the same cluster that showed mixed results were also scored equivocally.

Comprehensive scoring instruments like the ARCI, the POMS or the Drug Effect Questionnaire (DEQ) [17] can be subdivided into different subjective clusters (e.g. scale craving or scale alertness), but these subscales were not always reported separately. In these cases, the results of the composite scores were presented as part of the overall scale drug effect cluster for the DEQ and ARCI and the scale mood cluster for the POMS. A similar procedure was followed for driving tests. In some cases the effects on a driving task were reported as effects on separate CNS functions like divided attention, reaction time and motor function. These driving tasks were grouped accordingly. However, when an overall composite driving score was reported, driving tests were grouped under the cluster driving.

Categorization of alcohol concentration

The chance that a test will detect a difference from placebo is expected to increase with the alcohol concentration (measured through BAC and/or BrAC). To investigate this possibility, it was determined for each individual test whether the proportion of statistically significant effects increased with BAC/BrAC. In this way, the most frequently used tests and alcohol dosages could be compared for dose-dependency. For individual tests, the number of studies or the variability of alcohol concentrations were too small to determine meaningful dose–effect relationships. To obtain an overview of dose-effects, alcohol concentrations were pooled into 'lower', 'medium' and 'higher' levels. The levels were determined after inspection of the reported alcohol concentrations, but before relationships with pharmacodynamic tests were examined. The 'medium' level was chosen to be a BAC or BrAC of 0.5 g l^{-1}–0.7 g l^{-1}, because this resulted in an even distribution of studies across alcohol levels. This mid-range also included the legal driving limits for most Western countries, and it would be useful to show which functional biomarkers are able to detect alcohol effects at this legal level. The 'lower' and 'higher' levels were all BAC/BrACs outside the medium range. This approach allowed the identification of tests or clusters that showed a consistent response across studies and alcohol concentrations.

Several studies reported the effects of both ascending or descending alcohol concentrations. In these cases, we considered a certain test to be effective in detecting alcohol effects, when at least one of both limbs was significantly affected. In addition, it was the intention to evaluate the effect of increasing or decreasing alcohol levels on individual tests that showed a consistent dose–response relationship *and* were measured frequently enough.

Results

Study characteristics

General study characteristics are reported in Table 3.

Subject characteristics

The mean number of participants was 31 (23 males and eight females). The mean age of participants was not reported in 35% of the cases. The mean age for all remaining articles was 24.8 years (range 19–42 years).

Alcohol characteristics

In the majority of the cases (98%), alcohol was orally administered. In only 2% of all studies an intravenous administration procedure was described. Doses were not reported in 18 articles (8%). The calculated mean dose that was administered during trials was 0.69 g kg^{-1} (SD 0.25 g kg^{-1}). BrAC was measured in 199 studies (91%), whereas BAC was used as a parameter in only 13 studies (6%). Six studies (3%) reported both values jointly. BAC and BrAC were pooled together to calculate the mean alcohol concentration, which was 0.65 g l^{-1} (SD 0.20 g l^{-1}).

CNS tests

This review yielded 342 different tests to assess the acute CNS effects of alcohol. Table 4 shows a distribution of the

Table 3

Summary of general study characteristics

Blinding				Randomization		Design		Control	
Double-blind	Single-blind	Open	Unknown	Randomized	Non-randomized	Cross-over	Parallel	Baseline-controlled	Placebo-controlled
31%	46%	22%	1%	86%	14%	56%	44%	23%	77%

Table 4

Frequency distribution of 342 tests used in 218 acute alcohol studies

Frequency of use	Number of tests	%
>20	1	0.3
11–20	13	3.8
6–10	23	6.7
2–5	68	19.9
1	237	69.3

Table 5

Tests used more than 10 times

Test name	Number
Visual Analogue Scale (VAS): Scale Intoxication	26
Choice Reaction Time Task	16
Go/No Go Test	15
Profile of Mood States (POMS): Scale Depression/Dejection/Elation/(Positive) Mood	14
Digit Symbol Substitution Test (DSST)	13
Profile of Mood States (POMS): Scale Anxiety/Confidence/Unsure/Tension/Arousal/Composed	13
Pursuit Rotor Task	13
Beverage Rating Scale Scale Intoxication	12
Biphasic Alcohol Effects Scale (BAES): Scale Sedation	11
Biphasic Alcohol Effects Scale (BAES): Scale Stimulation	11
Profile of Mood States (POMS): Scale Anger/Friendliness/Hostility/Agreeable	11
Profile of Mood States (POMS): Scale Confusion/Vigour/Bewilderment/Activity/Clearheadedness	11
Profile of Mood States (POMS): Scale Fatigue/Inertia/Tired/Energetic	11
Subjective Intoxication Level	11

test frequencies across the literature search, indicating that a sizeable majority of all the described tests was used only once (69.3%) or no more than five times (89.2%). Tests that were used more than 10 times in the overall data-set are summarized in Table 5. This arbitrary cut-off was used to get an indication of the most frequently used tests. The results of such solitary tests cannot be used to draw general conclusions about acute alcohol effects. Only scale intoxication was used frequently enough (26 times) to allow an individual analysis of alcohol responsiveness, but in all other cases tests needed to be clustered to increase numbers sufficiently for a more general interpretation.

Clustered alcohol effects

Individual tests were grouped into predefined clusters in an attempt to facilitate the general interpretation of the results. Table 6 summarizes the progressive condensation of all individual tests into clusters with their corresponding CNS domains. Overall calculated significant alcohol effects [i.e. impairment/decrease (–), no significant change (=) or improvement/increase (+)] on each cluster are shown together with the publications in which these effects were described. Table 6 shows that alcohol mainly caused either no effect or functional impairments. Impairments were most pronounced in the clusters divided attention, digit symbol substitution test-like (DSST-like), motor control, postural stability, visuo-motor control, scale performance and in auditory/verbal memory: immediate recall. These clusters were reported frequently enough (>10 times) to allow some general interpretations. Saccadic eye movements were also impaired in 90% of all cases, but these were described only seven times.

Individual memory tests sometimes showed improvements in delayed recall or recognition (between 10 and 33%, Table 6), but never on tests of immediate or short term memory. In each of these studies, alcohol had been administered prior to the presentation of learning material. This is in line with the literature, which suggests that memory for information learned before the consumption of alcohol can be retroactively facilitated [18, 19].

Overall increases in effects were mainly found on the domain subjective experience. The clusters scale high and drug effect showed distinct increases in their subjective scores. In contrast, several different clusters of the subjective experience domain did not change much [marked as (=) in Table 6] following alcohol administration (e.g. scales aggression, alertness, calmness, mood and fatigue). The clusters production and semantics (language domain) were also hardly affected by alcohol. Because the effects of alcohol on the functional domain (neuro)endocrine and on several different clusters like production, scale depression, sleep, visual perception and electroencephalography alpha (EEG alpha) were reported in only a small number of studies (<10), solid conclusions cannot be drawn on the sensitivity of these functional biomarkers.

Dose–response relationships

The ability to show clear dose–response relationships is an important requirement for a meaningful drug–effect biomarker [7–11]. The dose also determines the sensitivity of a test for a drug, and the chance to detect an effect. Therefore, tests and clusters were examined for potential relationships to ethanol dose. An arbitrary cut-off of 10 reports per dose level for at least two levels was used to study the dose–response relationships for the most frequently reported clusters (Table 7). Divided attention, scale high and scale drug effect were among the most sensitive clusters to detect alcohol effects, since a majority of tests were affected at the lowest alcohol dose concentrations. Many test clusters showed an increased proportion of significant drug effects at higher doses (Table 7). The most convincing dose–response impairments were found for focused attention (7% of the tests within this cluster were impaired in the <0.5 g l^{-1} level, increasing to 62% at 0.5–

Table 6

Progressive condensation of all reported tests, into their corresponding clusters and domains (in grey)

Cluster	Test	(–)	(=)	(+)	References (frequency)
Language					
Production	Speech Performance, Speech Test, Voice Onset Time	33	67	0	[20–23] (*n* = 4)
Semantics	Backwards Reading Task (semantic priming), Lexical Decision Task, Mill Hill Vocabulary Test, Multiple Selective Vocabulary Test, Semantic Priming Task, Sentence Verification Task, Verbal Memory Task*, WAIS III: Vocabulary Test, Word Categorization Task	31	69	0	[24–34] (*n* = 11)
Attention					
Cluster	**Test**	**(–)**	**(=)**	**(+)**	**References (frequency)**
Divided attention	Choice Reaction Time Task (fixed sequences)*, Choice Reaction Time Task (random sequences)*, Choice Reaction Time Task integrated in Pursuit Rotor Task, Choice Reaction Time Task*, Critical Tracking Test (divided attention), Divided Attention Task, Driving Simulation Test (dual task), Primary Tracking Task with Secondary Visual Reaction Time, Pursuit Rotor Task combined with Visual Stimulus-Response Task, Saccadic Interference Task, Switching Attention Task, Tracking Input Manipulator*, Verbal-Manual Task, Visual Vigilance Task, VisuoSpatial Attention Task	68	29	3	[20, 21, 24, 25, 35–55] (*n* = 25)
DSST-like	Code Substitution Task, Digit Symbol Substitution Test (DSST), Digit Symbol Yes/No Test, Simple Letter Verification Task, Symbol Digit Substitution Test (SDST), Symbol Matching Task (reference key present during task), Verification Task	61	39	0	[24, 26, 27, 52, 56–70] (*n* = 19)
Flicker discrimination	Apparent Movement, Backward Masking, Bistable Stroboscopic Motion, Critical Flicker Fusion Test, Simultaneity Task, Velocity Perception Task	55	45	0	[71–76] (*n* = 6)
Focused/selective attention	Auditory Discrimination Task, Continuous Performance Task, Digit Span Task (forward), Go/No-Go Task, Go/No-Go Task*, Inspection Time Task, Letter Cancellation Task, Memory Scanning Test, Pattern Comparison Task, Perceptual Speed Task, Rapid Information Processing Task, Rapid Visual Information Processing Task, Signal Detection Task, Spatial Frequency Discrimination Test, Tachistoscopic Perception Task, Test d2, Vernier Discrimination Task, Visual Search Task, Visual Stimulus-Response Task (complex), Visual Stimulus-Response Task (complex), Visual Stimulus-Response Task (simple)	50	48	2	[24, 27–30, 44, 46, 52, 59, 63, 64, 68–72, 77–86] (*n* = 26)
Reaction time	Anticipation Timing Task, Auditory Discrimination Task*, Auditory Vigilance Task*, Choice Reaction Time Task, Choice Reaction Time Task (fixed sequences), Choice Reaction Time Task (random sequences), Complex Reaction Time Task*, Complex Reaction Time Test, Concept Identification Task, Concurrent Set Memory Task*, Continuous Performance Task (delayed memory)*, Continuous Performance Task (immediate memory)*, Continuous Performance Task*, Critical Tracking Test*, Digit Symbol Substitution Test (DSST), Digit Symbol Substitution Test (DSST)*, Digit Symbol Yes/No Test*, Divided Attention Task*, Driving Simulation Test (reaction time), Driving Simulation Test (dual task)*, Eriksen Flanker Test*, Fixed Set Memory Task*, Go/No Go Test (cued)*, Go/No-Go Task (high cognitive load)*, Go/No-Go Task (low cognitive load)*, Go/No-Go Task *, Go/No-Go Task*, Lexical Decision Task*, Memory Scanning Test*, Mill Hill Vocabulary Test*, Number Matching Pair Test*, Offset Reaction Time Task, Omitted Auditory Stimulus Task, Onset Reaction Time Task, Pattern Recognition Task*, Psychomotor Task, Pursuit Tracking Task (stressalyser)*, Rapid Visual Information Processing Task, Rapid Visual Information Processing Task*, Reaction Time Test, Reaction Time Test (acoustic stimulus), Reaction Time Test (optical sequence of stimuli) , Reaction Time Test (optical stimulus) , Reaction Time Test (optical/aucoustic stimuli), Reaction Time Test to Omitted Auditory Stimuli, Reaction Time Test to Omitted Tactile Stimuli, Reaction Time Test to Omitted Visual Stimuli, Repetition-Alternation Task (shape, color, location), Saccadic Interference Task, Signal Detection Test*, Simple Auditory RT Test, Simple Letter Verification Task*, Simple Reaction Time Task, Spatial Recognition Task*, Stop Signal Task*, Stroop Task*, Symbol Matching Task (reference key present during task)*, Tracking Input Manipulator*, Varied Set Memory Task*, Verification Task*, Vigilance Task (acoustic stimulus)*, Vigilance Task (optical stimulus)*, Vigilance Task*, Visual Reaction Time test, Visual Search Task*, Visual Stimulus-Response Task (during tracking), Visual Sustained Attention Task*, Visual Vigilance Task, Visual Vigilance Task*, VisuoSpatial Attention Task, Word Categorization Task*, Work Performance Series*	53	47	0	[24–26, 28, 30, 31, 35, 36, 38–44, 50–55, 59, 60, 63, 64, 67–71, 74, 76, 81, 83, 87–122] (*n* = 70)
Sustained attention (vigilance)	Auditory Vigilance Task, Continuous Attention Task, Continuous Performance Task (delayed memory), Continuous Performance Task (delayed memory)*, Continuous Performance Task (immediate memory)*, Number Matching Pair Test, Psychomotor Vigilance Task, Rapid Visual Information Processing Task, Serial Sevens Test, Signal Detection Test, Sustained Attention Task, Vigilance Task, Vigilance Task (acoustic stimulus), Vigilance Task (optical stimulus), Visual Sustained Attention Task, Visual Vigilance Task, Work Performance Series	43	57	0	[25, 26, 45, 55, 59, 81, 90, 91, 113, 114, 117, 123] (*n* = 12)

Table 6
Continued

Executive					
Cluster	**Test**	**(–)**	**(=)**	**(+)**	**References (frequency)**
Creativity	Purdue Creativity Test	0	100	0	[124] (*n* = 1)
Driving	Driving Simulation Test, Driving Simulation Test (drive only), Simulated Automobile Driving Task, Tracking Input Manipulator	100	0	0	[41, 55, 60, 125, 126] (*n* = 5)
Inhibition	Anticipation Timing Task, Antisaccadic Eye Movement Test, Balloon Analogue Risk Task, Barratt Impulsiveness Scale, Continuous Performance Task (delayed memory)*, Continuous Performance Task (immediate memory)*, Continuous Performance Task*, Covert Shift of Attention Task, Delay Discounting Test, Delayed Ocular Response Task, Eriksen Flanker Test, Experimental Discounting Task, General Knowledge Test, Gibson Spiral Maze test*, Go/No Go Test (cued), Go/No-Go Task, Go/No-Go Task , Go/No-Go Task (high cognitive load), Go/No-Go Task (low cognitive load), Iowa Gambling Task, Newman Perseveration Task, Pattern Comparison Task*, Question-based Delay Discounting Task, Recognition Task, Recognition Task (with context cues)*, Recognition Task (without context cues)*, Rectangular Maze Test*, Repetition-Alternation Task (shape, color, location), Risk-Taking Task, Signal Detection Task*, South Oaks Gambling Screen, Startle Response, Stop Signal Task, Stroop Task, Stroop Task: Negative Primes, Stroop Task: Positive Primes, Sustained Attention Task*, Tower of London*, Tracking Input Manipulator*, Visual Sustained Attention Task*	50	46	4	[24, 29, 35, 38, 41, 45, 50, 52, 59, 66, 67, 71, 72, 77, 82, 83, 87, 89–93, 95–98, 100, 104–108, 114, 119, 127–136] (*n* = 44)
Judgement	Choice Reaction Time Task*	50	50	0	[44] (*n* = 1)
Planning	Tower of London	100	0	0	[119] (*n* = 1)
Reasoning/association	Block Design Task, Categorization Task, Concept Identification Task, Conditional Associative Learning Task, Grammatical Reasoning Task, Logical Reasoning Task, Mathematical Processing Task, Mathematical Reasoning Task, Picture Arrangement Task, Picture Completion Task, Sentence Completion Task	55	45	0	[63, 64, 70, 80, 111, 123, 132, 137] (*n* = 8)
Set shifting	Go/No-Go Task*, Wisconsin Card Sorting Test	33	67	0	[30, 93, 138] (*n* = 3)
Spatial orientation	Card Rotations Task , Little Man Task, Manikin Task, Manikin Test	50	50	0	[59, 63, 64, 80] (*n* = 4)
Time/distance estimation	Choice Reaction Time Task*, Drawing Squares Test, Kinaesthetic Distance Estimation Test, Size Estimation Test, Speed Estimation Task (without speedometer), Temporal Discrimination Task, Time Estimation Task, Time Perception Task, Time Production Task, Visual Distance Estimation Task	46	46	8	[59, 76, 123, 139–142] (*n* = 7)
Working memory/immediate recognition	Auditory Memory Task, Backwards Reading Task, Choice Reaction Time Task*, Complex Reaction Time Test, Concentration Test, Concurrent Set Memory Task, Continuous Performance Task (delayed memory), Continuous Performance Task (immediate memory), Design Memory Task, Digit Span Task (backward), Fixed Set Memory Task, Letter-Number Test, Pattern Memory Test, Pattern Recognition Task, Recognition Task, Short Term Memory Task, Short-Term Memory for Words and Figures, Short-Term Memory Test, Spatial Memory Span Test, Spatial Recognition task, Spatial Working Memory Task, Sternberg Memory Scanning Task, Symbol Matching Task (reference key absent during task), Symbol Matching Task (reference key absent during task)*, Three Letters Task, Varied Set Memory Task, Visual Memory Task, WAIS-R: Digit Span Test (backward), Word Discrimination Task (immediate), Word Repetition Priming Task, X's and O's Task	53	47	0	[24, 27, 32, 63, 64, 67, 70, 71, 90, 91, 103, 116, 117, 119, 132, 143–147] (*n* = 20)

Memory					
Cluster	**Test**	**(–)**	**(=)**	**(+)**	**References (frequency)**
Auditory/verbal memory: delayed recall	Delayed Free Recall Test (words), Delayed Recall Task (words), Delayed Word Recall Task (24 h), Free Recall Task (words), Hopkins Verbal Learning Test (words), Logical Memory Test (story), Memory for Profile of Mood States (POMS) scores, Memory Task (8 letter-word pairs), Memory Task for Verbally Presented Words, Prose Memory Task, Recall for Mood States, Recall Task (names), Retroactive Interference Task (words), Wilde Intelligence Test (memory subset), Word List Learning (40 min. prior to alcohol intake), Word List Learning (immediately before alcohol intake)	40	30	30	[24, 25, 27, 34, 148–156] (*n* = 13)
Auditory/verbal memory: delayed recognition	Delayed Recognition Task (words), Hopkins Verbal Learning Test (words), Memory Task for Verbally Presented Words, Recognition of Depressive Mood States, Recognition of Elating Mood States, Recognition of Neutral Mood States, Recognition Task (names), Sentence Recognition Task (with context cues), Sentence Recognition Task (without context cues), Wilde Intelligence Test (memory subset), WMS-R: Paired Associates Learning (difficult), WMS-R: Paired Associates Learning (easy), Word Discrimination Task (delayed), Word List Learning (before alcohol intake), Word Recognition Memory Task, Word Recognition Task, Word Stem Completion Task (cued)	43	48	10	[24, 25, 33, 67, 128, 148, 150, 151, 153, 155, 157–159] (*n* = 13)
Auditory/verbal memory: immediate recall	Dichotic Listening Test, Free Recall Task (words), Immediate Recall Acquisition Task (words), Immediate Recall Task/Acquisition Task (words), Memory Task (words), Memory Task for Verbally Presented Words, Paired Associate Word Learning Task, Prose Memory Task, Verbal Immediate Memory Task (words), Verbal Short-term Memory Task (words)	67	33	0	[21, 24, 27, 32, 34, 49, 156, 158–162] (*n* = 12)
Implicit memory	Cued Incidental Learning (after alcohol intake), Cued Incidental Learning (before alcohol intake), Event Frequency Task, Frequency of Word Occurrence Task, Judgement of Frequency Task, Recall of Depressive Mood Sates, Recall of Elating Mood States, Recall of Neutral Mood States, Stem Completion Task (automatic processes), Word-Stem Completion Task, Word-Stem Completion Task (controlled processes)	33	40	27	[32, 33, 155, 157, 158, 161, 163–166] (*n* = 10)

Table 6
Continued

Memory					
Cluster	**Test**	**(–)**	**(=)**	**(+)**	**References (frequency)**
Learning	Verbal Memory Task*	100	0	0	[24] (*n* = 1)
Visual/spatial memory: delayed recall	Complex Figure Task, Delayed Memory for Geographical Map (with route), Emotional Memory Task	40	40	20	[40, 148, 167] (*n* = 3)
Visual/spatial memory: delayed recognition	Design Memory Task, Face Recognition Task, Picture Recognition Task	0	67	33	[18, 67, 150] (*n* = 3)
Visual/spatial memory: immediate recall	Benton Visual Retention Test, Complex Figure Task, Immediate Memory for Geographical Map (with route)	25	75	0	[85, 148, 167] (*n* = 3)
Motor					
Cluster	**Test**	**(–)**	**(=)**	**(+)**	**References (frequency)**
Motor control	Balance Beam Test, Choice Reaction Time Task*, Hand Steadiness Test (eyes closed), One Leg Stand Test, Reaction Time Test (acoustic stimulus)*, Reaction Time Test (optical sequence of stimuli)*, Reaction Time Test (optical stimulus)*, Reaction Time Test (optical/aucoustic stimuli)*, Standing Steadiness, Tapping Task, Tapping Task (non-dominant hand), Tapping Task (two hands)	61	39	0	[20, 21, 24, 25, 63–65, 76, 99, 103, 168, 169] (*n* = 12)
Postural stability	Body Sway, Body Sway (closed eyes), Body Sway (open eyes), One Leg Stand Test, Physical Activity Measurement (actiwatch), Sensory Organization Posturography Test, Steadiness Test, Walk and Turn Test	86	14	0	[30, 47, 49, 65, 74, 99, 168, 170–176] (*n* = 14)
Visuo-motor control	Bead String Test, Character Writing Test, Continuous Tracking Task (continuous instability), Continuous Tracking Task (frequent instability), Continuous Tracking Task (minor instability), Coordination Test Steering, Critical Tracking Test, Divided Attention Task*, Gibson Spiral Maze Task, Gibson Spiral Maze test, Hand Steadiness Test, Hand-Eye Coordination Test, Handwriting Analysis, Object Assembly Task, Pegboard Test, Primary Tracking Task, Pursuit Rotor Task, Pursuit Rotor Task Modified, Pursuit Tracking Task (stressalyser), Rectangular Maze Test, Signature Task, Speed Estimation Task (with speedometer), Spiral Maze Task, Tracking Input Manipulator*, Tracking Test, Tracometer, Visuomotor Integration Task	78	22	0	[24, 26, 30, 37–39, 41, 45, 49, 52, 53, 59, 65, 70, 79, 81, 88, 99, 113, 117, 120, 139, 142, 169–171, 177–190] (*n* = 40)
Neurophysiologic					
Cluster	**Test**	**(–)**	**(=)**	**(+)**	**References (frequency)**
EEG alpha	Electro-encephalography (EEG), Magneto-encephalography (MEG)	6	38	56	[191–197] (*n* = 7)
EEG beta	Electro-encephalography (EEG), Magneto-encephalography (MEG)	9	64	27	[192, 193, 196, 197] (*n* = 4)
EEG delta	Electroencephalography (EEG)	0	100	0	[197] (*n* = 1)
EEG theta	Electro-encephalography (EEG), Magneto-encephalography (MEG)	0	22	78	[193–197] (*n* = 5)
Evoked potential	Alternating Check Task, Categorization Task*, Choice Reaction Time Task*, Eriksen Flanker Test*, Event Related Potentials (ERP), Go/No-Go Task*, Memory Scanning Test, Odd Ball Paradigm, Vestibular Evoked Myogenic Potential Test, Visual Evoked Potentials, Visual Sustained Attention Task*, Watching 'Emotional' Pictures, Word Repetition Priming Task	52	21	27	[51, 87, 92, 94, 137, 144, 145, 198–206] (*n* = 16)
Eye movements	Binocular Balance Test, Oculomotor Functioning	100	0	0	[168, 207] (*n* = 2)
Eye movements – blink rates	Electro-oculography (EOG)	0	100	0	[114] (*n* = 1)
Eye movements – nystagmus	Caloric and Visual Supression Test, Electro-oculography (EOG), Horizontal Gaze Nystagmus, Vestibulo-Ocular Nystagmus Test	100	0	0	[170–172, 174, 199, 208] (*n* = 6)
Eye movements – pursuit	Oculomotor Functioning, Smooth Pursuit Eye Movement Task	67	33	0	[61, 168] (*n* = 2)
Eye movements – saccadic	Delayed Ocular Response Task, Oculomotor Functioning, Saccadic Eye Movement Test, Visuomotor Reading Task	90	10	0	[35, 61, 129, 168, 209–211] (*n* = 7)
Sleep	Multiple Sleep Latency Test (MSLT), Repeated Test of Sustained Wakefulness (RTSW), Sleep Latency, Sleep Test	40	60	0	[53, 212–214] (*n* = 4)

Table 6

Continued

Perception					
Cluster	**Test**	**(–)**	**(=)**	**(+)**	**References (frequency)**
Olfactory perception	Odor Discrimination/Odor Memory Test, Olfactory Ethanol Detection Test, Phenyl Ethyl Alcohol Detection Threshold Tests, University of Pennsylvania Smell Identification Test	50	50	0	[215] (*n* = 1)
Visual perception	Accomodation Task, Arden Plates, Binocular Vision Task, Contrast Sensitivity Chart, Depth Perception Task, Goldmann Visual Fields , IR Refractometer Task, Perceptual Vision Task, Rod and Frame Test (visual field dependence), Rotating Laser Drum Task, Snellen Acuity, Stereo Optical Stereo Tests, Stereoscopic Depth Perception, Subjective Vertical/Horizontal Test, TV Grating Contrast Sensitivity, Vision Test, Visual Contrast Sensitivity Test, Visual Field Test	52	48	0	[85, 110, 118, 201, 203, 216, 217] (*n* = 7)
Subjective experience					
Cluster	**Test**	**(–)**	**(=)**	**(+)**	**References (frequency)**
Scale aggression	Affect Inventory (Scale Anger/Sympathetic), Profile of Mood States (POMS) (Scale Agreeable/Hostile), Profile of Mood States (POMS) (Scale Anger), Profile of Mood States (POMS) (Scale Anger/Friendliness), Profile of Mood States (POMS) (Scale Anger/Hostility), Profile of Mood States (POMS) (Scale Friendliness), Subjective Effects of Alcohol Scale (SAES) (Scale Positive Social Influences), Visual Analogue Scale (VAS) (Scale Irritability)	8	75	17	[24, 30, 40, 58, 62, 83, 168, 175, 218–221] (*n* = 12)
Scale alertness	Affect Inventory (Scale Powerfulness/Energy), Biphasic Alcohol Effects Scale (BAES) (Scale Sedation), Profile of Mood States (POMS) (Scale Clearheaded/Confused), Profile of Mood States (POMS) (Scale Confusion), Profile of Mood States (POMS) (Scale Confusion/Bewilderment/Vigor/Activity), Profile of Mood States (POMS) (Scale Confusion/Vigour), Profile of Mood States (POMS) (Scale Vigour), Profile of Mood States (POMS) (Scale Vigour/Activity/Confusion/Bewilderment), Profile of Mood States (POMS) (Scale Vigour/Confusion), Sleep Questionnaire, Stanford Sleepiness Scale (SSS), Subjective Effects of Alcohol Scale (SAES) (Scale Sedation), Subjective Rating Scale (Scale Activity/Drowsiness), Subjective Rating Scale (Scale Alertness), Visual Analogue Scale (VAS) (Scale Alertness), Visual Analogue Scale (VAS) (Scale Drowsiness), Visual Analogue Scale (VAS) (Scale Sedation), Visual Analogue Scale (VAS) (Scale Sleepiness)	35	60	5	[24, 30, 40, 41, 53, 56, 58, 61, 62, 74, 76, 77, 83, 95, 133, 147, 149, 168, 175, 176, 198, 209, 213, 214, 218–221] (*n* = 28)
Scale calmness	Affect Inventory (Scale Afraidness), Affect Inventory (Scale Relaxedness), Biphasic Alcohol Effects Scale (BAES) (Scale Stimulation), Estimation of Mood Change Test (Scale Tense/Relaxed), Profile of Mood States (POMS) (Scale Anxiety), Profile of Mood States (POMS) (Scale Arousal), Profile of Mood States (POMS) (Scale Composed/Anxious), Profile of Mood States (POMS) (Scale Confident/Unsure), Profile of Mood States (POMS) (Scale Tension), Profile of Mood States (POMS) (Scale Tension), Profile of Mood States (POMS) (Scale Tension/Anxiety), Subjective Rating Scale (Scale Relaxation), Taylor's Manifest Anxiety Scale, Visual Analogue Scale (VAS) (Scale Nervousness), Visual Analogue Scale (VAS) (Scale Relaxedness), Visual Analogue Scale (VAS) (Scale Stimulatedness)	23	76	2	[24, 30, 40, 56, 58, 61, 62, 74, 76, 77, 83, 95, 100, 119, 133, 147, 149, 156, 158, 175, 176, 198, 214, 218–222] (*n* = 28)
Scale craving	Drug Effects Questionnaire (DEQ) (Scale Like), Drug Effects Questionnaire (DEQ) (Scale Like/Want More), Drug Effects Questionnaire (DEQ) (Scale Want More), Drug Effects Questionnaire (DEQ) Scale Like/Want More), Visual Analogue Scale (VAS) (Scale Desire), Visual Analogue Scale (VAS) (Scale Like), Visual Analogue Scale (VAS) (Scale Like/Dislike)	50	50	0	[56, 61, 62, 66, 74, 77, 82, 83, 96, 97, 105–107, 123, 127, 206, 218, 223] (*n* = 18)
Scale depression	Affect Inventory (Scale Depression), Profile of Mood States (POMS) (Scale Depression), Profile of Mood States (POMS) (Scale Depression/Dejection), Profile of Mood States (POMS) (Scale Elated/Depressed)	8	85	8	[30, 175, 218–221] (*n* = 6)
Scale dizziness	Visual Analogue Scale (VAS) (Scale Dizziness), Visual Analogue Scale (VAS) (Scale Lightheadedness)	100	0	0	[40, 74] (*n* = 2)
Scale drug effect	Addiction Research Center Inventory (ARCI) (Scale A), Addiction Research Center Inventory (ARCI) (Scale A/BG/MBG/LSD), Addiction Research Center Inventory (ARCI) (Scale A/BG/MBG/LSD/PCAG), Addiction Research Center Inventory (ARCI) (Scale A/BG/MBG/PCAG/LSD), Addiction Research Center Inventory (ARCI) (Scale A/BG/PCAG/LSD), Addiction Research Center Inventory (ARCI) (Scale A/M/MBG), Addiction Research Center Inventory (ARCI) (Scale A/M/MBG/PCAG), Addiction Research Center Inventory (ARCI) (Scale A/MBG/PCAG), Addiction Research Center Inventory (ARCI) (Scale BG/LSD), Addiction Research Center Inventory (ARCI) (Scale BG/LSD), Addiction Research Center Inventory (ARCI) (Scale MBG), Addiction Research Center Inventory (ARCI) (Scale PCAG), Addiction Research Center Inventory (ARCI) (Scale PCAG/A/LSD), Beverage Rating Scale, Drug Effects Questionnaire (DEQ) (Scale Drug Effect), Drug Effects Questionnaire (DEQ) (Scale Feel), Drug Effects Questionnaire (DEQ) (Scale Intoxication), Drunkenness Scale, Likert 'how drunk scale', Profile of Mood States (POMS) (Scale Intoxication), Subjective Effects Questionnaire (Scale Intoxication), Subjective Estimations of Intoxication, Subjective Intoxication Level, Subjective Judgement of Intoxication, Subjective Rating Scale (Scale Inebriation), Visual Analogue Scale (VAS) (Scale Drunkenness), Visual Analogue Scale (VAS) (Scale Feel), Visual Analogue Scale (VAS) (Scale Intoxication)	0	20	80	[26, 30, 35, 41, 49, 52, 56, 59–62, 66–69, 74, 77, 82, 83, 85–87, 95–97, 104–109, 114, 115, 123, 127, 134, 137, 138, 140, 145, 147, 166, 168, 171, 175, 180, 183, 190, 191, 197, 198, 206, 209, 218–221, 223–229] (*n* = 64)
Scale fatigue	Profile of Mood States (POMS) (Scale Energetic/Tired), Profile of Mood States (POMS) (Scale Energy), Profile of Mood States (POMS) (Scale Fatigue), Profile of Mood States (POMS) (Scale Fatigue/Inertia)	14	81	5	[24, 30, 40, 58, 62, 83, 218–221] (*n* = 10)

Table 6
Continued

Subjective experience					
Cluster	**Test**	**(–)**	**(=)**	**(+)**	**References (frequency)**
Scale high	Drug Effects Questionnaire (DEQ) (Scale High), Profile of Mood States (POMS) (Scale High), Subjective High Assessment Scale, Subjective High Assessment Scale (Scale High), Visual Analogue Scale (VAS) (Scale High)	0	13	87	[18, 56, 61, 62, 65, 66, 74, 80, 83, 96, 97, 105–107, 145, 194, 218, 219, 223] (*n* = 19)
Scale mood	Affect Inventory (Scale Surprisedness/Affection/Digust/Guilt/Sexuality/Humour/Happiness), Beck-Depression-Inventory (Scale Depression), Estimation of Mood Change Test (Scale Elated/Depressed), Mood Scale (Scale Pleasure/Activity/Dominance), Mood Sorting Test, Personality-Trait Presentation Task, Positive Affect/Negative Affect Schedule (Scale Negative Affect), Positive Affect/Negative Affect Schedule (Scale Positive Affect), Profile of Mood States (POMS) (Scale Depression), Profile of Mood States (POMS) (Scale Depression/Elation), Profile of Mood States (POMS) (Scale Depression/Elation/Positive Mood), Profile of Mood States (POMS) (Scale Elation/Positive Mood), Profile of Mood States (POMS) (Scale Mood), Profile of Mood States (POMS) (Scale Positive Mood), Profile of Mood States (POMS) (Scale Tension/Anxiety/Depression/Dejection/Anger/ Hostility/Vigour/Fatigue/Confusion/Bewilderment), Rotter's Internal-External Scale, Subjective Effects of Alcohol Scale (SAES) (Scale Negative Affect), Subjective Mood States (Scale Mood), Subjective Rating Scale (Scale Joyfulness), Subjective Rating Scale (Scale Positive Mood), Visual Analogue Scale (VAS) (Scale Contentedness), Visual Analogue Scale (VAS) (Scale Mood Changes), Visual Analogue Scale (VAS) (Scale Mood), Visual Analogue Scale (VAS) (Scale Pleasantness)	5	65	30	[24–26, 40, 52, 58, 59, 62, 74, 76, 83, 100, 119, 123, 133, 137, 149, 150, 156, 158, 168, 175, 195, 197, 221, 222, 229, 230] (*n* = 28)
Scale morality	Subjective Attitudes and Intentions to Drink and Drive	100	0	0	[227] (*n* = 1)
Scale performance	Affect Inventory (Scale Intelligentness), Alcohol Sensation Scale (Scale Impairment), Driving Questionnaire, Self-Evaluation of Performance , Subjective Estimations of Ability, Subjective Impairment Scale, Visual Analogue Scale (VAS) (Scale Driving), Visual Analogue Scale (VAS) (Scale Functional Integrity)	67	33	0	[26, 41, 45, 47, 48, 52, 59, 77, 120, 168, 175, 185, 227, 231] (*n* = 14)
Scale symptoms	Alcohol Sensation Scale (Scale Anaesthesia), Alcohol Sensation Scale (Scale Central/Warm/Dynamic/Periphery/Nausea), Alcohol Sensation Scale (Scale Sensations), Alcohol Sensation Scale (Scale Somatic Sensations), Drug Effects Questionnaire (DEQ) (Scale Nausea), Sensation Scale (Scale Physical Sensations), Sensation Scale (Scale Symptoms), Von Zerssen's List of Complaints (Scale Complaints)	42	58	0	[25, 56, 77, 175, 218, 229] (*n* = 6)
(Neuro)endocrine					
Cluster	**Test**	**(–)**	**(=)**	**(+)**	**References (frequency)**
Catecholamines	3-methoxy-4-hydroxy ethyleneglycol (MOPEG)	0	0	100	[232] (*n* = 1)
Cortisol/ACTH	ACTH, cortisol	0	43	57	[56, 191, 218, 233, 234] (*n* = 5)
Other neuroendocrine substances	AVP, β-endorphin, cholecystokinin, dopamine, melatonin, prolactin, serotonin	14	71	14	[233–236] (*n* = 4)
Sex hormones	3α-hydroxy-5α-pregnan-20-one-like progesterones, allopregnanolone, DHEA, DHEA-S, estradiol, estradiol/estrone/progesterone, luteinizing hormone (LH), pregnenolone, progesterone, testosterone	27	64	9	[56, 218, 234] (*n* = 3)

The overall cluster effects are reported together with the articles in which they are reported. '+' reflects an improvement or increase, '=' reflects no significant effect and '–' reflects an impairment or decrease as measured by the corresponding test. Whenever tests provided different parameters with information on more than one functional domain, effects were scored separately, and the secondary effects were marked (*). Some tests were reported more than once within the same reference (e.g. at several dose levels).

0.7 g l^{-1} and 74% with levels >0.7 g l^{-1}), divided attention, reaction time, inhibition, working memory and visuo-motor control. Clear dose-related effects were also found for the cluster scale drug effect.

We made efforts to evaluate the effect of increasing and decreasing alcohol concentrations on individual tests that showed a consistent dose–response relationship and were reported frequently enough. Unfortunately, only few of these studies addressed this issue. We therefore restricted our review to the main objective of creating an overview of the most sensitive CNS tests to measure the acute effects of alcohol.

All 15 scales of the cluster subjective high that were tested at the 0.5–0.7 g l^{-1} level increased after alcohol administration. Although they were only tested nine times under high dose circumstances throughout the studies, all observed subjective high scales were affected by alcohol at this level. The effects on other frequently reported clusters described in Table 7 either increased hardly with dose (e.g. evoked potential and scale craving) or were not clearly

Table 7

Dose–response relationships for clusters tested at least 10 times (except for values between brackets) with at least two dose levels

Executive									
	<0.5 g l^{-1}			0.5–0.7 g l^{-1}			>0.7 g l^{-1}		
Cluster	**(–)**	**(=)**	**(+)**	**(–)**	**(=)**	**(+)**	**(–)**	**(=)**	**(+)**
Inhibition	32	65	3	56	41	3	64	29	7
Working memory	18	82	0	39	61	0	75	25	0
Attention									
	<0.5 g l^{-1}			0.5–0.7 g l^{-1}			>0.7 g l^{-1}		
Cluster	**(–)**	**(=)**	**(+)**	**(–)**	**(=)**	**(+)**	**(–)**	**(=)**	**(+)**
Divided attention	58	33	8	67	33	0	79	21	0
Focused/selective attention	7	86	7	62	38	0	74	26	0
Reaction time	23	77	0	51	49	0	73	27	0
Motor									
	<0.5 g l^{-1}			0.5–0.7 g l^{-1}			>0.7 g l^{-1}		
Cluster	**(–)**	**(=)**	**(+)**	**(–)**	**(=)**	**(+)**	**(–)**	**(=)**	**(+)**
Visuo-motor control	43	57	0	85	15	0	89	11	0
Subjective experience									
	<0.5 g l^{-1}			0.5–0.7 g l^{-1}			>0.7 g l^{-1}		
Cluster	**(–)**	**(=)**	**(+)**	**(–)**	**(=)**	**(+)**	**(–)**	**(=)**	**(+)**
Scale alertness	19	78	4	53	42	5	41	53	6
Scale calmness	20	80	0	21	75	4	31	69	0
Scale craving	50	50	0	58	42	0	(38)	(63)	(0)
Scale drug effect	0	41	59	0	7	93	0	9	91
Scale high	0	36	64	0	0	100	(0)	(0)	(100)
Scale mood	7	71	21	0	64	36	8	58	33
Perception									
	<0.5 g l^{-1}			0.5–0.7 g l^{-1}			>0.7 g l^{-1}		
Cluster	**(–)**	**(=)**	**(+)**	**(–)**	**(=)**	**(+)**	**(–)**	**(=)**	**(+)**
Visual perception	–	–	–	36	64	0	60	40	0
Neurophysiologic									
	<0.5 g l^{-1}			0.5–0.7 g l^{-1}			>0.7 g l^{-1}		
Cluster	**(–)**	**(=)**	**(+)**	**(–)**	**(=)**	**(+)**	**(–)**	**(=)**	**(+)**
Evoked potential	50	25	25	54	23	23	(50)	(13)	(38)

Results are in % per alcohol dose concentration. '+' reflects an improvement or increase, '=' reflects no significant effect and '–' reflects an impairment or decrease

dose-related (scale calmness, scale mood and scale alertness). While visual perception was only occasionally reported across different research groups, a mild dose-related deterioration was observed at the highest dose level.

Discussion

A large number of tests are used in the literature to measure the acute CNS effects of alcohol, even for the same effect. As with similar reviews for other drug classes [7–11], there were even more tests than articles: 342 in 218 publications. Almost 70% of all reported tests were only used once, and close to 90% were used five times or less. This lack of standarization limits the comprehension of the effects of drugs on the CNS. For alcohol, this is complicated further by complex (saturable) pharmacokinetics (with large intersubject variability related to induction of clearance, sex and other genetic factors), tolerance and withdrawal effects, drug and food interactions and differences between patient populations (alcoholics, drug abusers, social anxiety disorder, etc.). Understanding these complexities, and their functional consequences for social and problematic drinking, would be facilitated by the use of a limited number of well-characterized biomarkers for

different alcohol effects, reflecting a range of relevant functions. With this background, tests were grouped into test clusters and functional domains. Prior reviews indicate that this technique served as a helpful tool in evaluating functional biomarkers for other drug effects [7–11]. Although this methodology inevitably led to the loss of certain information, it resulted in a structured and comprehensive overview of the CNS effects of alcohol.

As far as possible, we used neuropsychological compendia [12, 13] to group all the tests into related test clusters and functional CNS domains. Still, some categorization we undertook might seem arbitrary. The short memory test for example, was captured under executive functions instead of memory (as one might expect from the test name). Although this seems confusing at first sight, it is completely in line with the neuropsychological compendia we used. These authors state that the short memory test should be considered as a working memory (or executive) task rather than a pure memory task, because it is governed by brain areas that are also related to planning, organizing and time orientation. Longer-term memory tests in a stricter sense require much more hippocampal activity.

Tests within the most sensitive clusters as shown in Table 6, which also show a clear dose–response relationship as shown in Table 7 are considered most valuable. Thus, divided attention tests (i.e. attention domain), visuo-motor control tests (i.e. motor domain) and subjective drug effect tests (i.e. domain subjective effects) are the most sensitive functional biomarkers for the acute effects of alcohol on the CNS in healthy volunteers (at least according to the results of our review). Most clusters of the attention domain were clearly affected by alcohol. The cluster divided attention showed a higher sensitivity to alcohol compared with clusters like reaction time and focused attention, since these tests could detect lower alcohol concentrations. Tests within the divided attention cluster are more complex than those measuring simple reaction time or focused attention, and it is likely that lower doses of alcohol will have a larger impact on a more complex task than on a simpler version. Tests within the cluster reaction time can still be useful biomarkers, since 73% showed impairments at higher alcohol concentrations (>0.7 g l^{-1}), but they are less suitable to measure the impact of lower exposure. Similarly, executive clusters like working memory and inhibition are also quite capable of detecting alcohol effects at high doses (on average in 75% and 64% of the cases, respectively).

Alcohol clearly impaired the three clusters of the motor domain, but only visuo-motor control tests were reported frequently enough at the different dose levels to allow a dose–response analysis. Although the effects on motor control and postural stability look promising, these tests can only be considered validated CNS-biomarkers for alcohol effects if dose–response relationships are established. Alcohol effects on visuo-motor control were identified at concentrations >0.5 g l^{-1} and a dose-dependent impairment was observed. The cluster visuo-motor control fulfilled the criteria as a useful functional biomarker.

Scales of subjective high and drug effects were by far the most sensitive clusters in the subjective experience domain. Both scales increased dose-dependently, and showed effects in over 90% of the cases in the highest dose category. Many different subjective scales (or scale variants) are currently used in literature to measure subjective alcohol experience, but this review shows that only a few of these scales (subjective high and drug effects) are actually able to measure accurately the subjective effects of alcohol. Scales of calmness, mood and alertness seem to be less sensitive to alcohol.

The sensitivity of many clusters could not be assessed, because they were not reported frequently enough to allow an accurate evaluation (e.g. critical flicker fusion, visual perception and all the (neuro)endocrine clusters), although some of these uncommon clusters showed promising results (e.g. saccadic eye movements, EEG alpha and EEG theta). Clusters like semantics and scale aggression do not seem to be valuable biomarkers for alcohol effects, because the majority of the tests show no effect after alcohol administration in healthy volunteers. Some clusters showed significant overall alcohol effect in only a modest proportion of studies, like inhibition (50%) and working memory (53%). These executive tasks were measured frequently enough to allow a subdivision according to dose levels, which revealed larger percentages in the highest dose category of >0.7 g l^{-1} (64 and 75%, respectively). This indicates that alcohol effects (particularly at higher doses) can be masked for clusters that do not contain enough tests across the different doses to allow dose categorization. An important issue concerning tests within clusters like immediate recall (auditory/verbal memory), working memory and visuo-motor control is that all these functions may be affected by attention and concentration [12]. Attention tasks show an effect in 73–79% of cases at higher alcohol doses. Divided attention was even more sensitive, yielding significant results at low doses in over half the cases. The strong influence of alcohol on attention should be taken into account when looking at the results of other test clusters and functional domains that rely on attention.

Despite its infrequent appearance throughout our search, all tests assessing overall driving performance (i.e. cluster driving) were impaired by alcohol. Driving performance is an executive task that to a large extent relies on (visuo-)motor control and focused/divided attention. The most sensitive functional biomarkers to detect alcohol effects at the average legal driving level (i.e. the medium dose level) include tests of visuo-motor control as well as scales of subjective high and drug effect, followed by focused and divided attention. For visuo-motor control, the pursuit rotor task (a tracking task) was the most appropriate

method to detect alcohol effects around the driving limit, at least in a laboratory setting. It is not surprising therefore, that all of the 10 driving tests included in our review showed an effect of alcohol, including the two cases that studied the effects of a low dose. Reaction time is another aspect of driving, but individual reaction time tests only showed an impairment at medium levels in only half of the cases. This function seems less suitable to demonstrate the impact of alcohol on driving proficiency in a medico-legal setting.

In summary, the most sensitive functional biomarkers for the acute CNS effects of alcohol that were identified in this review are divided attention, focused attention, visuomotor control, scale high and scale drug effect. Furthermore, reaction time, working memory and inhibition are also considered useful, but only at higher alcohol doses. Driving tasks also seemed to be sensitive to even low concentrations of alcohol, but this complicated setup was not used very frequently in the literature. The impairing effects of alcohol on the clusters DSST-like, motor control, postural stability and immediate recall (auditory/verbal memory) are noteworthy, but clear dose–effect relationships could not be established.

This review describes a systematic literature search aimed to assess the sensitivity and usefulness of functional biomarkers to demonstrate acute CNS effects of alcohol in healthy volunteers. The results of this review may be helpful in selecting rational biomarkers for studies investigating the acute CNS effects of alcohol or for future alcohol–interaction studies. The results also show that many different biomarkers are currently used, when a certain CNS effect of alcohol is studied, and that such studies would greatly benefit from a certain degree of standardization.

Competing interests

There are no competing interests to declare.

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